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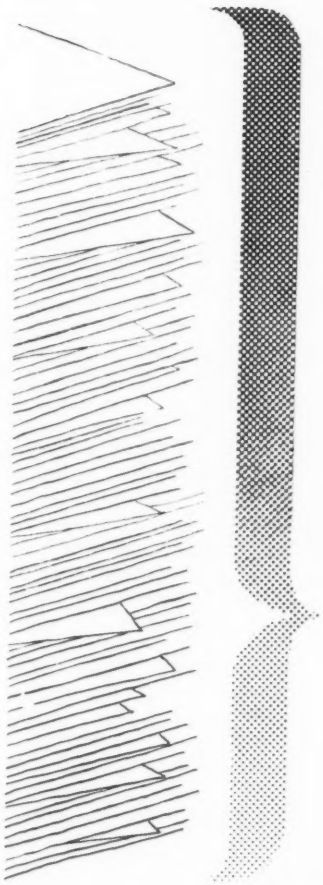

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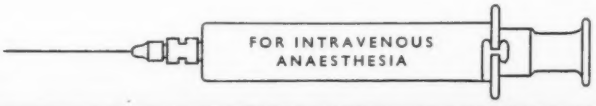

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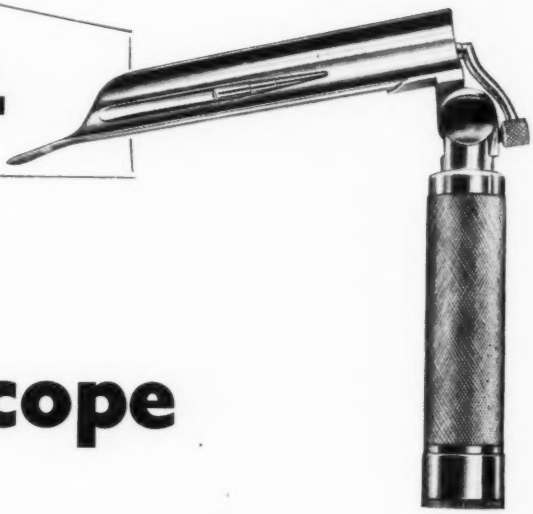

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VOL. XXIX, No. 2 FEBRUARY 1957

EDITORIAL

THE PROBLEM OF PAIN RELIEF

IT is just over 150 years since Sertürner isolated morphine from opium. During this period and in spite of the introduction of a number of "opioids", morphine has retained its place as one of the most useful drugs in the pharmacopoea. From the first, however, physicians have appreciated the dangers as well as the benefits of such a powerful central nervous depressant, and the good which has resulted from its introduction has vastly outweighed the evil. Today we are fortunate to have at our disposal a number of drugs which will suppress, at least temporarily, some of the effects of overdosage with morphine and similar drugs. We may look, therefore, to the increased use of opiates to prevent postoperative pain, administered perhaps in conjunction with respiratory stimulants such as amiphenazole. The adequate control of postoperative pain has proved to be as elusive as the fabled Baaras, which " recedes from the hand of him who would take it "; many have pursued this object by different and devious routes, and one is reminded of the doctrine of Ralph Waters, that the control of pain costs a certain price, which is not greatly different whatever means be used. We would not discourage anaesthetists from attempting to gain such a desirable end as a pain-free awakening for their patients, but we would enjoin caution in the pursuit.

Already the first flush of enthusiasm for nalorphine is passing off, and it has been noticed that the reversal of morphine overdose with it may only be temporary. Furthermore, we know of at least one case in which it seemed that convulsions were precipitated by the use of nalorphine in dosage which, at the time, did not seem grossly excessive. No case of convulsions has yet been reported after the use of amiphenazole, but it does produce electroencephalographic evidence of cortical stimulation, similar to the " spikes " seen in epilepsy. Caution, therefore, seems to be indicated in the use of this drug until we are more familiar with its side effects.

The whole question of the reversal of the preponderant action of one drug by the administration of another is one which ought to give no pause, for every antidote has a number of actions, some desirable and others not. Although the body is a complex mechanism which is normally held in balance by a multitude of delicate devices, this balance is apt to be disturbed in ill health, and it is on such people, whose control mechanisms are disturbed, that antidotes are most likely to be called for, and in which they are most likely to do harm by producing unexpected and undesirable side effects.

The anaesthetist must avoid as many pitfalls as he can by employing reading, the antidote to ignorance, and experience, the antidote to credulity. Unfortunately, the experiences of a lifetime are all too few to provide a safe " Highway Code "; and it is only by cultivating scepticism that the accumulated experiences of anaesthesia, gathered in the journals, can be applied for the benefit of patient and physician alike. Let us learn all we can and apply our knowledge cautiously, regarding each new fact with scepticism until experience proves it true, and thus we shall attain confidence, and a measure of success, built upon the failures and successes of others. To these others we owe thanks, whether for bothering to write of their successes or for daring to speak of their failures; to all anaesthetists we would say, " Read, but also write, so that you may not only learn, but also contribute your quota of experience to the general pool."

Brit. J. Anaesth. (1957), **29**, 50

PHARMACOLOGY AND PHAEOCHROMOCYTOMA

BY

R. A. MILLAR

Department of Anaesthesia, Montreal Neurological Institute, Canada

FRÄNKEL (1886) identified bilateral tumours of the adrenal medulla at the postmortem of a girl of eighteen years who died in syncope, but the first description of the syndrome of paroxysmal hypertension associated with phaeochromocytoma was not recorded until 1922 (Labbé et al., 1922). In the following year an unsuccessful attempt was made at removal of a phaeochromocytoma found at operation (Masson and Martin, 1923). A correct antemortem diagnosis was reached by Vaguez and Donzelot in 1926. Although a pre-operative diagnosis had not been made, tumours were excised by Roux (1926) and Mayo (1927). Pincoffs and Shipley (1929) are credited with the first successful diagnosis and removal of an adrenal medullary tumour.

Most chromaffin tumours, so called because they assume a yellow-brown colour when treated with potassium dichromate (Henle, 1865), occur in the adrenal medulla as phaeochromocytomata (*phaios*—dusky; *chrōma*—colour). Extra-adrenal sites (Kohn, 1903) are less frequent (10–15 per cent), the term "paraganglioma" usually being employed for tumours in the embryonic organ of Zuckerkandl, in the lumbar or thoracic paravertebral spaces, in and around the great abdominal vessels, in the coeliac ganglion, the carotid or aortic bodies, in the glomus jugularis, and for the extremely rare chromaffin tumours within the cranial cavity. It is reasoned that there is little justification for differentiating adrenal and extra-adrenal sites of origin, and that any adrenaline or noradrenaline secreting tumour should be considered as a phaeochromocytoma (Symington and Goodall, 1953).

Tumours of chromaffin tissue (chromaffinomas) are rare. In patients presenting with hypertension their incidence appears to be as low as 0.5 per cent (Smithwick, 1946; Graham, 1951); however, in the United States alone the condition may account for 600–800 patients annually (Graham, 1951). In about 30 per cent of patients with phaeochromocytoma the classical presenting feature, hypertension, is paroxysmal (Green, 1946; Goldenberg et al., 1950) but hypertension is not invariably present (Alwall and Wulff, 1948; Goodall and Symington, 1953; Henry, 1954); also, tumours may occur without producing other clinical evidence of increased hormone production (Spatt and Grayzel, 1948). An extremely rare accompaniment is secondary adrenal insufficiency (McGavack et al., 1942). True malignancy is infrequent (less than 10 per cent) and all tumours without metastases are probably benign (McGavack et al., 1942; Symington and Goodall, 1953). In about 10 per cent of patients with phaeochromocytoma the tumour is bilateral. Multiple tumours are frequently found in children (Cahill and Aronow, 1949).

Tumours of the adrenal medulla present a clinico-pathological picture which has been aptly summarized as histologically benign and physiologically malignant (Apgar and Papper, 1951). The cytopathological aspects have been considered by Geschickter (1935), Blacklock et al. (1947), and Symington and Goodall (1953). The widely varied clinical features of phaeochromocytoma, "the great mimic" (DeCourcy and DeCourcy, 1952) are described in numerous case reports and review articles, to which the interested reader is referred. The references cited here are representative only: MacKeith (1944); Blacklock et al (1947); Cahill (1948); Smithwick et al (1950); Graham (1951); DeCourcy and DeCourcy (1952).

MECHANISM OF HYPERTENSION IN PHAEOCHROMOCYTOMA

At birth and during early infancy the adrenal medulla contains considerably more noradren-

aline than adrenaline (Shepherd and West, 1951; West et al., 1953). Phaeochromocytoma in childhood is usually accompanied by severe and sustained systolic and diastolic hypertension (Goodall and Symington, 1953). By adult life the relative proportions of noradrenaline and adrenaline in the normal gland are reversed to about 15 per cent and 85 per cent respectively, but most adrenal medullary tumours contain predominantly noradrenaline (Holton, 1949; Goldenberg et al., 1949). Studies showing that adrenaline can be formed from noradrenaline by adrenal extracts (Bulbring, 1949), and by the isolated adrenal gland (Bulbring and Burn, 1949), suggest that the immature tumour cells of a phaeochromocytoma may be unable to carry out the normal process of methylation.

Ample evidence is available of the differing circulatory effects of adrenaline and noradrenaline (Goldenberg et al., 1948; Barcroft and Konzett, 1949; Swan, 1949; Barnett et al., 1950; Barcroft and Starr, 1951). When the two amines are infused in mixtures containing equal proportions the adrenaline effects apparently predominate; some of the physiological effects of noradrenaline are counteracted by much smaller amounts of adrenaline (De Largy et al., 1950).

The majority of patients with phaeochromocytomata show marked increases in systolic and diastolic pressures, as expected with noradrenaline, but uniform agreement between the expected action of the predominant hormone secreted (from urinary estimations) and the clinical picture is not always obtainable. A tentative classification of different clinical types of phaeochromocytoma, based on the quantitative estimation of catechol amines in a number of adrenal medullary tumours has been put forward, however (Goldenberg et al., 1950).

While the clinical features of phaeochromocytoma are conveniently regarded as being due solely to the intermittent or continuous discharge of adrenaline and noradrenaline, this explanation is probably too simple; generalized sweating, for example, one of the outstanding features, is not easily explained on this basis.

The interesting problem presented by patients who show persistent hypertension after removal of an adrenal medullary tumour could be resolved on the basis of a secondary mechanism, which might also explain the hypertension occurring in those phaeochromocytoma patients who display a negative response to the adrenergic blocking agents (Goldenberg and Aronow, 1905). Prolonged infusions of sympathomimetic amines in animals have failed to induce persistent hypertension after the infusion is stopped; with large doses of adrenaline (Erlanger and Gasser, 1919; Prohaska et al., 1937) or noradrenaline (Blacket et al., 1950) the initial level of hypertension may not even be maintained. Studies on human subjects, to one of whom an adrenaline infusion was administered on twelve successive days, showed that the slope of the pressure response curve was unaltered, although there was a distinct increase in the subjective limit of tolerance (Green et al., 1948).

There is insufficient evidence to support the view of Calkins et al. (1950) that stimulation of the pituitary-adrenal axis might be a factor in sustained hypertension after tumour removal. Similarly, possible correlations between persistent hypertension and renal histological changes appear inconclusive (Green, 1946; Fertig et al., 1951; Goodall and Symington, 1953).

An interesting observation by Peart (1954) that two patients with sustained postoperative hypertension had earlier shown the usual hypotension immediately following tumour removal does not necessarily exclude the possibility of a secondary (neurological) mechanism.

According to Peart (1954), there is no evidence that the length of history, severity of symptoms, the size or amine content of the tumour, the adrenaline/noradrenaline ratio, rate of amine excretion, or renal damage, are associated with persistent hypertension after operation.

A consideration of all the evidence, including the suggestion that essential hypertension and phaeochromocytoma may co-exist in the same patient, suggests that the concept of sustained hypertension secondary to a chromaffin tumour may be in the category of " not proven ". The opinion has been recently expressed that " recorded cases are all explicable on other grounds or are insufficiently documented " (Symington and Goodall, 1953).

ADRENALINE TOXICITY

Studies initiated by the Medical Research Council following the first world war showed in anaesthetized dogs that a state similar to shock could follow cessation of an infusion of large doses of adrenaline (Bainbridge and Trevan, 1917). Circulatory collapse and death apparently resulted from diminished circulating blood volume, leading to a steady fall in blood pressure in spite of peripheral vasoconstriction.

Apnoea accompanying pulmonary oedema, and cardiac arrest (sometimes following a period of arrhythmias while the blood pressure was still high), were also implicated in death from adrenaline overdosage. This work was confirmed in anaesthetized (Lamson and Keith, 1916; Henderson et al., 1917; Erlanger and Gasser, 1919; Freeman, 1933) and in conscious dogs (Freeman et al., 1941), which could be protected from fatal circulatory collapse by transfusion with blood or hypertonic glucose.

Raab (1948), emphasizing an increase in myocardial oxygen consumption out of proportion to the increase in coronary flow, inferred that myocardial anoxia played an important role in adrenaline toxicity. This seems unlikely in face of the fact that although adrenergic blocking agents markedly protect against the lethal effects of adrenaline, they do little to antagonize the action of sympathomimetic amines on cardiac force and rate (Nickerson, 1949).

Nickerson and Goodman (1947) observed, in small animals injected with toxic doses of adrenaline, that anoxic convulsions and apnoea occurred before cardiac arrest. Survival time was prolonged by artificial ventilation but eventually pulmonary oedema developed and respiratory exchange became ineffective. It has been shown that increases in pulmonary arterial and venous pressures occur after large doses of adrenaline (Hamilton et al., 1939); the protection offered by dibenamine and other adrenergic blocking drugs may be to prevent dangerous rises in systemic pressure with secondary effects on the pulmonary circulation (Nickerson and Goodman, 1947). Another factor in the toxicity of adrenaline may be central or reflex chemoreceptor inhibition after large doses (Gernandt, 1946). In the patient with a phaeochromocytoma (aside from collapse during major or minor surgery) death is usually a result of cerebral haemorrhage, pulmonary oedema, or ventricular fibrillation (Wood, 1950).

HYPOTENSION AFTER TUMOUR REMOVAL

It is well established that hypotension and vasodilatation follow the termination of infusions of adrenaline (Koehler et al., 1937; Green et al., 1948) and of noradrenaline (Goldenberg et al., 1948; Blacket et al., 1950; Barnett et al., 1950; Peart, 1954).

A comparable mechanism is held to be responsible for the acute hypotension which follows ligation of the vascular pedicle of an adrenal medullary tumour. Similar hypotensive episodes are not infrequent, however, in the course of relatively minor operations on patients harbouring undiagnosed phaeochromocytomata. The danger is well illustrated by the series of 125 patients reviewed by Graham (1951); 33 had died as a result of attempts at tumour removal.

Bartels and Cattell (1950) attributed operative hypotension to acute left sided cardiac failure resulting from an excess of circulating adrenaline; this would seem to be a more likely mechanism in the period before tumour removal and a serious hazard in the patient with an undiagnosed phaeochromocytoma. Hypotension is usually associated with ligature of the vascular supply of the tumour and with the complex cardiovascular adjustments which must necessarily follow a precipitate drop in the blood levels of adrenaline and noradrenaline.

Adrenal cortical dysfunction cannot be excluded in patients with medullary tumours before and after tumour removal (Neff et al., 1942; Richards and Hatch, 1951; Hubble, 1951). Adrenaline, in doses within the physiological range, stimulates adrenal cortical activity in animals, with depletion of ascorbic acid (Vogt, 1944; Long and Fry, 1945; Nasmyth, 1950); hypertrophy of the cortex has also been reported (Vogt, 1945). This effect is thought to be induced by an action of adrenaline on the hypothalamus leading to liberation of A.C.T.H. However, the evidence for a similar mechanism in man is controversial (Vogt, 1955; Hunter et al., 1955).

DRUG	DOSE
Histamine acid phosphate (Roth and Kvale, 1945)	I.V., 0.01–0.05 mg in 0.5 ml saline
Methacholine chloride (mecholin; mecholyl chloride) (Guarneri and Evans, 1948)	S.C.I., 10–25 mg
Tetraethylammonium chloride (etamon chloride) (La Due et al., 1948)	I.V., 300–500 mg
Dibenamine (Spear and Griswold, 1948)	I.V., 7 mg/kg in 300 ml 5% glucose saline
Dibenzyline (dibenyline; SKF 688A)	I.V., 0.5–2.0 mg/kg in 300 ml 5% glucose saline
Benzodioxanes (933 F; piperoxan, benodaine) (Goldenberg et al., 1947)	I.V., 0.25 mg/kg or 10 mg/sq metre
Tolazoline (Priscol; tolazine; priscoline; benzazoline) (Console et al., 1950)	I.V., I.M., orally, 25–100 mg
Phentolamine (regitine, rogitine) (Emlet et al., 1951)	I.V., I.M., 5 mg; orally, 25–50 mg

PHARMACOLOGICAL AIDS IN THE DIAGNOSIS OF PHAEOCHROMOCYTOMA (*v.* TABLE)

Drugs employed in the diagnosis of phaeochromocytoma can be placed in two categories:

(1) Those which provoke an episode of paroxysmal hypertension.

(2) Those which induce hypotension by antagonizing the peripheral effects of circulating pressor amines.

(1) The first group includes histamine, mecholin, and the tetraethylammonium compounds. Histamine was first used by Mayo (1927) in an attempt to abort a hypertensive crisis; the ability of the drug to induce paroxysmal hypertension was later demonstrated (Hyman and Mencher, 1943). Roth and Kvale (1945) developed the histamine test as the first pharmacological aid in the diagnosis of phaeochromocytoma. It is recorded that histamine stimulates adrenaline secretion in dogs (Wada et al., 1940), but the mode of action of this group of drugs is not established. There seem to be at least five possible mechanisms which could be implicated:

(*a*) Sympathetic stimulation induced by a carotid and aortic sinus mechanism secondary to the transient initial fall in blood pressure which occurs with these drugs in the patient with a phaeochromocytoma. In the case of the tetraethylammonium ion, however, it has been been shown that part of its ganglion blocking action (Acheson and Moe, 1946) is to prevent the release of adrenaline from the normal adrenal medulla (Morrison and Farrar, 1949).

(*b*) Increased vascularity of the adrenal medulla secondary to arteriolar and capillary dilatation (LaDue et al., 1948).

(*c*) A stimulant nicotine action, fleeting and unimportant in the normal state, may act as a trigger mechanism for the preganglionic cholinergic fibres supplying an adrenal tumour.

(*d*) A direct effect of chemical agents on the cells of the adrenal medulla.

(*e*) Paralysis of the compensatory reflex mechanisms (autonomic ganglia, carotid and aortic sinuses) which normally buffer a rise in blood pressure (LaDue et al., 1948; Page and Taylor, 1950). It is of considerable clinical importance that the hypertension produced by adrenaline and noradrenaline is greatly potentiated by previous blockade of ganglionic transmission (Page and Taylor, 1947, 1950; Moe, 1948; Bartorelli et al., 1954).

The precipitate rise in blood pressure produced by drugs in this group, with accompanying severe headache and acute anxiety, have frequently caused concern; more serious effects, e.g. multifocal ventricular extrasystoles, have also been reported (Gould and Mundal, 1951). Lowering the legs and other postural changes may suffice to prevent a dangerous pressor effect; placing the patient on a tilting table would be a useful safeguard. However, routine testing with hypertensive agents does not now apppear justifiable; their

use is probably best reserved for patients showing paroxysmal hypertension, where hypotensive drugs are less useful. When employed, an effective adrenaline blocking drug should be at hand (in addition atropine may be required if methacholine chloride is used).

(2) The second group of drugs comprises the adrenergic blocking agents.

Dale (1933) introduced the term "adrenergic" to designate those agents which induce responses from sympathetically innervated effector cells. "Adrenergic blocking agent" refers to compounds which specifically inhibit certain responses of effector cells to adrenaline, related amines, and sympathetic nerve impulses. Nickerson (1949) has pointed out that the terms "adrenolytic" and "sympatholytic" (Bacq and Fredericq, 1934) are misnomers, since neither nerve ending, nor chemical mediator, nor effector cell is "lysed" by these agents. In addition, any sharp distinction between "adrenolysis" and "sympatholysis" appears to be artificial. All adrenergic blocking agents appear to be more effective against circulating sympathomimetic agents than against responses to sympathetic nerve activity.

Adrenergic blocking agents of clinical importance can be classified in four groups: β-chloroethylamines (dibenamine and dibenyline); benzodioxane compounds (e.g. piperoxan), ergot alkaloids; and the imidazoline derivatives (tolazoline and phentolamine). Although all these compounds show a reasonably specific adrenergic blocking action, their different behaviour results from direct actions on various tissues, which renders their classification in one group impossible. Fortunately, in the field of adrenergic blockade, there do not appear to be any qualitative differences between the responses of man and laboratory animals (Nickerson, 1949).

The probable relationship between chemical structure and adrenergic blocking activity has been discussed (Nickerson, 1949); some early views on the mode of action of adrenergic blocking drugs deserve mention. A polarizing action on effector cells, limiting the penetration of circulating adrenaline without affecting the activity of intracellular mediators, was postulated by Rosenblueth and Cannon (1936) to explain the "adrenolytic" action of piperoxan. The suggestion, based on *in vitro* studies by Morison and Lissak (1938), that this drug might act by accelerating the destruction of adrenaline, is not tenable on clinical grounds since the *in vitro* inactivation of adrenaline was slow even in the presence of piperoxan. These and other similar suggestions have been discussed (Raab and Humphreys, 1946; Nickerson, 1949), but little is known of the precise mode of action of any of the adrenergic blocking agents. In the case of dibenamine, a highly effective "adrenolytic" compound and the one most frequently studied, there appear to be two stages in the development of blockade. Firstly, an approximation of the drug to near the site of action of adrenaline, where a state of competitive equilibrium may exist, and where the blocking agent can be rendered ineffective by further doses of adrenaline. Secondly, chemical binding of the blocking agent to a cellular constituent, which prevents further equilibration with adrenaline, and may account for the completeness and duration of the blocking action of adrenaline (Nickerson, 1949; see also Harvey and Nickerson, 1954). In addition, duration of action of dibenamine may be partly determined by the slow release of the drug from fatty depots into the blood stream (Axelrod et al., 1952).

An interesting and uniform characteristic of the adrenergic blocking agents is their failure to block the increases in cardiac force and rate induced by adrenaline. This applies to dibenamine (Nickerson and Goodman, 1947; Hecht and Anderson, 1947); to the ergot alkaloids (Dale, 1906) and their dihydrogenated derivatives (Rothlin, 1947); to tolazoline (Ahlquist et al., 1947) and phentolamine (Hecht et al., 1950); and to the benzodioxane compounds (DeVleeschhouwer, 1935), although these are also direct myocardial depressants (Nickerson, 1949).

Adrenaline induced hyperglycaemia is inhibited by the adrenergic blocking agents to a varying degree. Relatively ineffective in this respect are dibenamine (Nickerson and Goodman, 1947; Hecht and Anderson, 1947) and tolazoline, although this drug may itself induce hyperglycaemia directly (Hermann and Vial, 1942). Phentolamine (Trapold et al., 1950; Hecht et al., 1950), the ergot alkaloids (Rothlin, 1925) and their dihydrogenated derivatives (Rothlin, 1947) all

inhibit the rise in blood sugar produced by adrenaline. Some idea of the complexities involved in accurate studies with these agents is revealed by the fact that the benzodioxane drugs, although they inhibit adrenaline induced hyperglycaemia, may confuse the issue by stimulating the sympatho-adrenal system (Bovet and Simon, 1937). Harvey et al. (1952) found no correlation between the ability of adrenergic blocking agents to inhibit hyperglycaemia and their ability to suppress pressor responses.

Dale demonstrated in 1906 that extracts of ergot reverse or abolish the effects of adrenaline injected intravenously, but the ergot group and the dihydrogenated ergot alkaloids, e.g., dihydroergokryptine and dihydroergocornine (Freis et al., 1948; Wilkins et al., 1950; Barcroft et al., 1951), have not gained wide clinical acceptance for the diagnosis of a chromaffin tumour. The dihydrogenated ergot alkaloids although less toxic than the parent compounds (Rosenblueth and Cannon, 1933), appear to depress vasomotor reflexes through the brain stem in doses smaller than those necessary for sympathetic blockade (Bluntschli and Goetz, 1948). The yohimbine derivatives, although effective adrenergic blocking agents (Yonkman et al., 1944), have not merited clinical usage.

DIBENAMINE

This compound, chemically closely related to the nitrogen mustards, was first noted by Eisleb (1934) but was not studied in detail until 1947. In animals, intravenous dibenamine (10–20 mg per kg) reversed the pressor action of adrenaline over a wide range (0.1μg–10 mg adrenaline per kg). The "adrenolytic" action was evident five to ten minutes after intravenous injection, reaching a maximum in about thirty minutes, the effect persisting for from thirty-six hours to five days (Nickerson and Goodman, 1947).

Well marked reversal of the pressor action of adrenaline by dibenamine is infrequent in man, probably because of the smaller dosage employed. After dibenamine, the response to adrenaline usually consists of mild systolic hypertension, diastolic hypotension, tachycardia, and increased stroke volume; cardiac output is therefore increased (Hecht and Anderson, 1947).

In accord with other adrenergic blocking agents, sympathetic nerve impulses are less readily blocked than effects directly attributable to injected adrenaline (Nickerson and Goodman, 1947), but "sympatholytic" effects, e.g., nasal congestion and pupillary constriction, accompany effective "adrenolytic" doses in man. Administered alone, dibenamine may produce slight systolic and diastolic hypotension, with an increase in peripheral blood flow; pupillary constriction sometimes persists for several days (Hecht and Anderson, 1947).

The chief toxic effects of the nitrogen mustards, viz. central excitation, local tissue destruction, and a toxic effect on the bone marrow, have not been a dangerous problem with slow intravenous injection of dibenamine in the range of dosage employed clinically. However, recorded side effects such as nausea, vomiting, restlessness, dizziness, mental confusion, and venous irritation with thrombophlebitis, occur in perhaps 65 per cent of patients, and a convulsive seizure following dibenamine injection in man has also been reported (Hecht and Anderson, 1947). Marked postural hypotension, maximal within six hours of injection, may be detectable for as long as two days, indicative of persistent blockade of compensatory vascular reflexes. This can be effectively counteracted by elastic bandages applied to the legs, or with large abdominal binders.

Unfortunately, oral administration of dibenamine is insufficiently safe; due to its directly irritant properties, nausea and vomiting occur before evident signs of adrenergic blockade (Hecht and Anderson, 1947).

The overall effectiveness of dibenamine can be summarized by stating that once an adequate block has been established it cannot be overcome by massive sympathetic stimulation or by large doses of sympathomimetic amines (Nickerson, (1949).

The more recent β-chloroethylamine derivative, dibenyline, is safe and satisfactory by the oral route (Fellows et al., 1954; Boyd, 1956). This drug has a greater oral and intravenous potency than dibenamine, with an improved therapeutic ratio. Several patients with adrenal medullary tumours have been successfully controlled with oral dibenyline in doses of about 20 mg four times

daily (Allen et al., 1951; Haimovici et al., 1951). For general clinical use dibenyline has largely displaced dibenamine; the pharmacological and clinical effects of the two drugs are qualitatively very similar (Duff, 1956).

BENZODIOXANE DERIVATIVES

Studies by Fourneau and Bovet (1933) showed that piperoxan was " adrenolytic " in animals in doses from 0.25–2 mg per kg. Increased dosage depressed and finally abolished the carotid and aortic sinus reflexes; the maximum tolerated dose (above 10 mg per kg) produced sympathetic paralysis (DeVleeschhouwer, 1935; Heymans and Bouckaert, 1935; Jourdan and Galy, 1939; Bing and Thomas, 1945). The pressor response to adrenaline was decreased, abolished, or reversed depending on the relative dose level.

In man, Goldenberg et al. (1947) obtained an effective reduction in the pressor response to infusions of adrenaline and noradrenaline, a finding which has not been consistently confirmed in other hands (Prunty et al., 1950). In the phaeochromocytoma patient piperoxan usually produces a fall in blood pressure of up to fifteen minutes duration (usually shorter). In essential hypertension, a moderate rise in pressure is to be expected, probably indicative of central stimulation (Goldenberg et al., 1947). Occasionally the resulting hypertension is abrupt and excessive (Drill, 1949); encephalopathy (Green and Peterson, 1950) and acute pulmonary oedema (Rosenheim, quoted by Swan, 1951) have been reported following piperoxan injection. Severe reactions have been observed in about 8 per cent of essential hypertensives (Wilkins et al., 1950). In large doses the piperoxan may produce anaesthesia (Handovsky, 1948).

IMIDAZOLINE DERIVATIVES

Tolazoline is related chemically and pharmacologically to the sympathomimetic amines and to histamine, but the actions of the drug are complex. Some effects appear to be sympathomimetic, e.g. cardiac stimulation, coronary vasodilatation, and gastro-intestinal inhibition; other actions suggest a cholinergic mechanism. Although better known as a peripheral vasodilator, tolazoline is an effective " adrenolytic " compound, reversing (in animals) the pressor action of adrenaline, although the myocardial stimulation and coronary dilatation induced by adrenaline may actually be enhanced by tolazoline (Ahlquist et al., 1947). The drug has been effectively employed as a therapeutic hypotensive agent during removal of a phaeochromocytoma, when some increase in bronchial secretions was noted (Console et al., 1950).

Greater potentialities in the diagnosis and therapy of phaeochromocytoma are offered by phentolamine, which was synthesized in 1947 by Marxer and Miescher of Ciba Laboratories (Meier and Yonkman, 1949). Phentolamine was found to be " adrenolytic " in animals (Meier et al., 1949) and in man (Hecht et al., 1950); a " sympatholytic " effect was obtained with doses about twice those required to abolish the pressor action of adrenaline (Herrold et al., 1949). The onset of action was more rapid but of shorter duration than with dibenamine (Warren et al., 1949).

In dogs the pressor response to adrenaline and to noradrenaline is effectively blocked (Moyer et al., 1953). In man the cutaneous vasoconstriction and central effects of adrenaline are apparently not affected. Large doses of phentolamine (1–1.5 mg per kg) administered intravenously to normal and hypertensive human subjects produce moderate hypotension and tachycardia (Longino et al., 1949).

Side effects of phentolamine comprise nasal congestion, lachrymation, pupillary constriction, nausea, sweating abdominal cramps and diarrhoea (Hecht et al., 1950). However, a sensation of warmth with flushing of the skin are usually the only effects noted after intravenous injection of 5 mg, the optimal dose recommended for the diagnosis or therapy of phaeochromocytoma (Emlet et al., 1951; Gifford et al., 1952). Given intravenously, the effects of phentolamine are largely dissipated in one or two hours (Hecht et al., 1950). With intramuscular use effects appear in thirty to forty minutes and persist for two or three hours. With repeated oral doses symptoms become less noticeable and the drug appears to be well tolerated in repeated doses of 25–100 mg four-hourly (Longino et al., 1949).

In summary, phentolamine is superior to dibenamine for clinical use, in that it produces adrenergic blockade within five minutes after

intravenous administration, is relatively nontoxic regardless of the route of administration, and is effective by mouth (Trapold et al., 1950).

All sedatives and narcotics should be omitted during the twenty-four hours preceding a pharmacological test for phaeochromocytoma. The safest agent is phentolamine 5 mg intravenously, a positive result being indicated by a fall in blood pressure of greater than 35 mm Hg systolic and 25 mm Hg diastolic, occurring within two minutes of injection and persisting for at least two minutes (Gifford et al., 1952). Piperoxan may subsequently be employed to confirm a positive phentolamine test, 20 mg of piperoxan being injected over two minutes into a saline infusion. A positive result is indicated by a prompt fall in blood pressure, returning to the basal level in five minutes.

ESTIMATION OF CATECHOL AMINES IN BLOOD AND URINE

The estimation of an increased content of adrenaline-like substances in a blood sample withdrawn from a patient with an adrenal medullary tumour was reported by Beer et al. (1937), Strombeck and Hedberg (1939), and Hyman and Mencher (1943). Volhard (1944) and Raab and Smithwick (1949) were unable to confirm these findings, and it is doubtful whether available chemical methods were sufficiently accurate or specific. Modern chemical methods for the estimation of adrenaline and noradrenaline concentration, based on the formation of fluorescent condensation or oxidation products, are in process of assessment (Lund, 1950; Weil-Malherbe and Bone, 1953; Euler and Floding, 1955a); however, such methods should detect increases in catechol amine concentration as far above the physiological range as would be expected during a hypertensive crisis.

The highly specific biological procedures—such as that described by Crawford and Outschoorn (1951)—may be used if facilities are available, but in general they are time-consuming and outside the scope of the clinical laboratory.

Because of the paroxysmal nature of adrenal medullary discharge in many patients, false negative results from analysis of peripheral plasma are to be expected.

The diagnostic value of urinary estimations of adrenaline and noradrenaline was first pointed out by Engel and Euler (1950), and confirmed by Goldenberg and Rapport (1951). The following figures are an approximate guide to the noradrenaline concentrations in urine over twenty-four hours (Goldenberg, 1954):

0–50 μg in normals.

0–100 μg in patients with essential hypertension (in this group two-thirds of patients showed normal values).

Above 100 μg in patients with phaeochromocytoma (usually 600–2700 with persistent hypertension; 190–1530 with paroxysmal hypertension).

With specific techniques of estimation, two distinct procedures are involved: firstly, the separation of adrenaline and noradrenaline from tissue extracts; secondly, estimation—chemically, by a fluorimetric technique—biologically, utilizing a pharmacological test preparation.

The method of chromatographic adsorption on a column of aluminium oxide or hydroxide, introduced by Shaw (1938), allows a quite specific removal from plasma or urinary extracts of compounds containing a catechol nucleus. Catechol amines, thus separated, are eluted from the column by means of acetic or hydrochloric acid. If a chemical technique is to be used, the fluorimetric method of Lund (1950) probably offers the most adequate specificity for the estimation of adrenaline and noradrenaline in tissue extracts. A recent modification appears to allow an accurate determination of noradrenaline and adrenaline in urine (Euler and Floding, 1955b) without including possible catechol degradation products; the latter seriously interfere with the use for urine of the other currently employed fluorimetric technique, the controversial method of Weil-Malherbe and Bone (1953). As a rapid screening procedure it may suffice to use a hydrolysed urine sample, but for more complete specificity it is necessary to prepare an extract.

For biological assay, a urine extract must be carefully prepared, concentrated to a small volume, and neutralized (Euler and Hellner, 1951; Euler and Orwen, 1955; Goldenberg et al., 1954). The test preparation usually employed for noradrenaline is the blood pressure of the rat (Crawford and Outschoorn, 1951) or the cat (Euler,

1949). For adrenaline the rat uterus (Gaddum and Lembeck, 1949) or fowl rectal caecum (Euler, 1949) can be utilized.

If facilities are available, paper chromatography may be utilized as a diagnostic aid (James, 1948; Goldenberg et al., 1949). When 0.05 ml of an acid-alcohol extract of normal urine is applied to paper the amounts of adrenaline and noradrenaline are too small to become visible, the lower limit of detection being about 1 μg. A rough quantitative guide to the activity of a phaeochromocytoma may be obtainable from the appearance of the adrenaline and noradrenaline spots which should be clearly visible when a urinary extract is chromatographed (Goldenberg et al., 1954).

A rapid screening procedure for hypertensive patients has been described (Moulton and Willoughby, 1955); a similar technique was earlier mentioned by von Euler (1951). Urine is passed into a clean jar containing 50 mg ascorbic acid; the sample is stored in the refrigerator until assay, which utilizes the cat blood pressure on which neutral samples of untreated urine may be tested.

West (1952) has suggested the following treatment of adrenal medullary tumours removed at operation, prior to assay of the catechol amine content. Minced portions of the tumour or metastases are placed in a weighed container with 0.01N hydrochloride acid in the accurate proportion of 10 g tumour to 3 ml acid. The specimen is refrigerated and sent to the pharmacologist for assay.

If chrome fixation alone is required the tumour may be placed in equal parts of 5 per cent potassium dichromate and 10 per cent neutral formalin (Symington and Goodall, 1953).

MANAGEMENT OF THE PATIENT WITH PHAEOCHROMOCYTOMA

Adequate pre-operative care of the patient with an active adrenal medullary tumour resembles, and is as important as, the care afforded the patient undergoing thyroidectomy for toxic goitre.

Preparation to combat adrenaline intoxication should include a full diet to build up reserves of liver glycogen (Symington and Goodall, 1953); a high salt content has also been recommended (Biskind et al., 1941). Interference with adrenal cortical function may be counteracted with intramuscular cortisone 25–50 mg twice daily, with D.O.C.A. 5 mg daily, for two days pre-operatively.

Adrenergic blocking agents should be given as required. Phentolamine, in oral doses of 25–75 mg, four- or six-hourly, is safe and easily managed (Longino et al., 1949); a hypertensive crisis can be aborted by intravenous phentolamine, 5 mg. In the immediate pre-operative period the same drug may be continued intramuscularly or intravenously. Severe or sustained hypertension may be an indication for the use of dibenamine 2 mg per kg intramuscularly two hours before operation, or 7 mg per kg dissolved in 300 ml glucose saline and given intravenously over one hour (Spear and Griswold, 1948). Dibenyline may be preferable, 0.5–2 mg per kg, infused over one hour.

In severe cases the clinical picture might be confused by additional premedication other than atropine. If " adrenolytic " drugs are not employed pre-operatively, routine premedication, preferably with barbiturates, or a method of " stealing " the adrenal, can be utilized, depending on a careful pre-operative assessment by the anaesthetist.

If the site of a phaeochromocytoma is known, adequate access is usually obtainable through a posterolateral kidney incision, with resection of the 12th rib if necessary. A bilateral transverse upper abdominal incision is favoured where the site of the tumour is indefinite (Cahill and Aronow, 1949).

A more ambitious surgical technique has been recommended, involving two operating teams; paravertebral incisions are centered over the 12th ribs, the paravertebral segments of the 11th and 12th ribs being removed to give simultaneous bilateral exposure of the adrenal glands, with opportunity for sympathectomy if adrenal exploration is negative (Young, 1936; Richards and Hatch, 1951).

Postural tachycardia and hypotension (systolic and diastolic) were observed to be especially marked in patients with phaeochromocytoma (Smithwick et al., 1950). Change of position should be regarded as a highly critical manoeuvre

in these patients both pre-operatively, when a hypertensive crisis may result, and especially in the period following excision of the tumour. This is emphasized by a reported fatality resulting from circulatory collapse incidental to turning a patient from the prone to the supine position (Thompson and Arrowood, 1954).

Hypotension and circulatory failure immediately following tumour removal is counteracted by blood transfusion and vasoconstrictor therapy, e.g. infusion of noradrenaline, 2 mg of active base, or phenylephrine 40 mg, per litre of glucose saline solution. In certain clinics 500 ml of blood is always given before tumour removal, continuing subsequently as required (Thompson and Arrowood, 1954).

It has been shown that the vasoconstrictor action of noradrenaline is only maintained in the presence of cortisone and allied compounds (Fritz and Levine, 1951; Ramey et al., 1951). "The corticoids bestow on the tissues the capacity to react efficiently to internal or environmental stimuli but are not themselves those stimuli" (Vogt, 1955). Hydrocortisone, 100 mg in a slow infusion of 500 ml of 5 per cent glucose solution, or adrenal cortical extract 10 ml per hour may therefore be given for the first twenty-four hours after operation. Cortisone 50 mg intramuscularly, as required, and D.O.C.A. 5 mg might also be indicated.

Goldenberg (1954) has emphasized the resistance of these patients to the pressor effects of noradrenaline, because of its hyperbolic concentration-action curve, on the upper limit of which large doses must be given before any increased effect is produced. The decreased sensitivity to adrenaline and noradrenaline appears to outlast removal of the tumour for several days, although the initial onset of hypotension is immediate; doses of noradrenaline up to 100 μg per minute may be required to maintain a good pressure level post-operatively (Goldenberg, 1954; Peart, 1954). There is good evidence to suggest that the normal response of the peripheral vascular bed to sympathomimetic amines is dependent in some measure on adrenal cortical hormones, especially the 11-oxygenated steroids (Zweifach et al., 1947; Cleghorn et al., 1950; Raab et al., 1950; Kurland and Freedberg, 1951; Fritz and Levine, 1951). Without further evidence, the possibility that adrenocortical dysfunction may be concerned in hypotension following removal of an adrenal medullary tumour can hardly be evaluated.

It should be remembered that adrenergic blocking agents administered pre-operatively may prevent an early return of critical cardiovascular regulatory reflexes, especially those concerned in postural adjustments. The effects of dibenamine, for example, may be noticeable for as long as seventy-two hours after administration (Spear and Griswold, 1948). For this reason, pre-operative "adrenolytic" therapy is not always recommended (Goldenberg, 1954), and experience has shown that removal of a phaeochromocytoma can be successfully accomplished without the use of adrenergic blocking agents (Thompson and Arrowood, 1954).

Heroic resuscitative measures after tumour removal have been adversely criticized on the grounds that drugs given at this time merely enhance an existing degree of acute left-sided cardiac failure (Bartels and Cattell, 1950). These workers suggest that the Trendelenberg position alone will suffice to protect from severe hypotension which, they claim, is only temporary. A consideration of the literature does not support the view that conservative treatment alone would be successful in all cases.

Infusions of noradrenaline should be closely supervised, and discontinued as early as possible, because of the troublesome skin lesions which may result (Greenwald et al., 1952; Kurland and Malach, 1952; Uricchio et al., 1953). In one series nearly 50 per cent of patients infused with noradrenaline showed local venospasm, skin pallor, and cyanosis around the area of injection, appearing one to twenty-four hours after the start of the infusion. A red, streaky phlebitis, with vesicular eruptions and superficial ulcerations, were noted in several instances, although complete healing soon occurred. One patient, however, developed a deep skin ulcer (for which grafting was later required) although there had been no obvious leakage of noradrenaline extravascularly (Kurland and Malach, 1952). Superficial spreading gangrene, for which amputation was required, has also been reported (Uricchio et al., 1953). Infusions of potent vasoconstrictor agents are

best given in a forearm vein; the hands and feet, and the legs in patients with diabetes or peripheral vascular disease, should be avoided if possible. Hot packs at and above the site of injection have been successfully employed as a precautionary measure (Kurlan and Malach, 1952).

The management and course of anaesthesia in patients with adrenal medullary tumours is described in many papers, of which the following are examples: Walton (1950); Apgar and Papper (1951); Ward et al. (1952); Cobb et al. (1953); Harrison and Seward (1954); Thompson and Arrowood (1954); Wordsworth (1955).

ANAESTHESIA AND THE ADRENAL MEDULLA

On theoretical grounds, choice of anaesthetic agent for the patient with phaeochromocytoma should depend on the degree to which any agent affects or is affected by the liberation of blood concentrations of adrenaline and noradrenaline outside the physiological range. A consideration of the literature, however, exposes a remarkable and perhaps revealing conflict between experimental evidence and clinical application.

It should be remembered that while anoxia or hypercarbia may precipitate a hypertensive crisis a fall in blood pressure may act in similar fashion by stimulation of pressor receptors. Thiopentone, for example, should be used with special care (Dundee, 1956).

Spinal analgesia has only rarely been recommended for removal of a phaeochromocytoma (e.g. DeCourcy and DeCourcy, 1952), but total sympathetic blockade by high spinal analgesia, with resulting inhibition of reflex adrenaline and noradrenaline secretion, has much in its favour provided that severe hypotension is avoided.

Few anaesthetists would support without qualification a published opinion that the technique of anaesthesia has no bearing on postoperative collapse (Biskind et al., 1941). Improved chemical methods for the estimation of both adrenaline and noradrenaline may provide more direct information about the suitability of different techniques. In one reported series, anaesthesia (with diverse agents) produced rises in plasma catechol amine concentration, but these were outmatched by the gross increases induced by surgical manipulation of the tumour (Manger et al., 1954).

It cannot be too strongly emphasized that selection of premedication and anaesthetic technique is less important than an adequate understanding of the physiological principles underlying correct management of the patient with a phaeochromocytoma (Apgar and Papper, 1951; Thompson and Arrowood, 1954).

ETHER

Elliott, in 1912, drew attention to the sympathomimetic properties of diethyl ether. This has received substantial clinical support, while evidence deduced from animal experiments is not lacking (Schlossmann and Mugge, 1929; Bhatia and Burn, 1933; Phillips and Freeman, 1933; Elmes and Jefferson, 1942; Corbett, 1942; Johnson, 1949; Brewster et al., 1952, 1953; Watts, 1955). In small laboratory animals there is definite evidence of adrenaline liberation during surgical operations under ether anaesthesia (Vogt 1952).

It is well established that ether, in common with other general anaesthetics, is a direct myocardial depressant (Cattell, 1923; Olmsted and Ogden, 1929; Bhatia and Burn, 1933; Bennett and Fisher, 1948; Woods et al., 1949; Fisher et al., 1951; Prime and Gray, 1952; Price and Helrich, 1955). Blalock (1927), on the other hand, found increases in cardiac output in dogs during surgical anaesthesia with ether, a finding difficult to reconcile with the direct cardiac effects of ether unless, for instance, it is postulated that depression in the heart-lung preparation is balanced by simultaneous liberation of adrenaline from the adrenal medulla of the intact animal. Such a postulation, based on careful experiments on dogs before and after adrenalectomy, was put forward by Brewster et al. (1953), who considered that the reflex adrenal medullary stimulation produced by ether resulted in the release of approximately 1 μg adrenaline per kg per minute. According to these workers, this was a major factor in the safety of ether anaesthesia.

It should be noted that studies on the effects of anaesthetics on the heart-lung preparation may be initiated in the presence of an increased plasma

catechol amine concentration produced both by the agonal release of endogenous adrenaline and noradrenaline, and by the infusion of adrenaline which may be employed to prevent deterioration of the preparation. For example, infusion of 0.5–1 μg adrenaline per minute did not prevent 61 per cent depression of cardiac function at a blood ether concentration of about 90 mg per cent a level close to that accompanying light surgical anaesthesia in the dog (Price and Helrich, 1955).

The liberation of 1 μg adrenaline per kg per minute, as suggested by Brewster et al. (1953), in the absence of gross differences in tissue uptake, diffusion, or destruction, might increase the peripheral blood concentration of adrenaline to about 14 μg per litre; at this level, it would be expected, signs of adrenaline intoxication should be conspicuous. Furthermore, it is difficult to imagine that adrenaline liberation in counteracting myocardial depression would not frequently "overshoot", inducing marked degrees of systolic hypertension, diastolic hypotension, or cardiac arrhythmias (which are quite infrequent during uncomplicated ether anaesthesia in man).

Studies carried out by the writer have suggested that infusion of 2 μg adrenaline per minute, in a conscious human subject, yields detectable increases in adrenaline concentration in peripheral venous plasma, although there is little or no change in blood pressure measured by the auscultatory method. 3 μg per minute is sufficient to induce circulatory effects typical of adrenaline, with accompanying blood levels in the region of 0.3 μg per litre (this estimate may be slightly too low, because of limitations in the method of measurement). In one subject, infusion of 6 μg per minute (0.11 μg per kg per minute) increased peripheral plasma levels to 1.4 μg adrenaline per litre, a concentration close to this being obtained in the same subject during insulin hypoglycaemia (Millar, 1956). Definite evidence pointing to blood levels even of this order during ether anaesthesia in normal human subjects is lacking (Hammond et al., 1956).

The possibility cannot be excluded that the irritant properties of ether per se may produce adrenaline secretion, for intra-aortic injections of 0.1 ml of ether have recently been shown to produce a marked increase in apparent adrenaline output, as estimated by a chemical method, although control values were also raised above levels presently accepted by pharmacologists (Woods et al., 1955). This finding disagrees with the work of Brewster et al. (1953), which showed that after adrenalectomy the circulatory stimulant action of ether was absent.

It is in deep anaesthesia that an adrenaline effect on the heart would be most needed, since it has been shown that myocardial depression is linearly related to increasing blood ether concentrations. But it seems unlikely that in deep anaesthesia liberation of adrenaline by a reflex mechanism could be other than depressed.

From clinical experience systolic hypertension is infrequent during either light or deep anaesthesia of several hours duration, when a technique employing high gas flows (about 10 litres per minute) is adopted with no rebreathing. Moderate degrees of systolic hypotension are frequent, especially in the deeper planes, but clinical evidence suggests that regulation of blood pressure is related more to maintenance of circulating blood volume than to any effect of ether itself.

There appears to be general agreement that few serious effects ascribable to the sympathomimetic action of ether occur in patients with phaeochromocytoma (Thompson and Arrowood, 1954; Apgar and Papper, 1951). In fact, increased depth of ether anaesthesia has been successfully utilized to suppress hypertensive crises occurring during operation (Thompson and Arrowood, 1954).

In summarizing this complex picture at the present time the following opinion based on available evidence may be offered. Firstly, blood adrenaline levels during ether anaesthesia in man may sometimes be increased to a statistically significant degree, but this is probably only one facet of the complex compensatory mechanisms operating to maintain circulatory function during ether anaesthesia. Secondly, reflex liberation of adrenaline in surgical anaesthesia of greater than moderate depth is difficult to accept although a direct effect of high concentrations of ether on the adrenal medullary cells (unlikely in man) cannot be excluded. Thirdly, there is no evidence that ether is unduly toxic to the patient with a tumour of the adrenal medulla. Finally, the question remains of the unresolved role played by

the adrenal cortex both in experimental studies on animals and in anaesthetized man under clinical conditions (Hammond et al., 1956).

ADRENALINE-INDUCED ARRHYTHMIAS UNDER ANAESTHESIA

Goodman Levy (1912, 1913, 1914, 1919; Levy and Lewis, 1912) stressed the dangers of adrenaline injection during chloroform anaesthesia; provided that anaesthesia was maintained in the lighter planes, remarkably small doses of adrenaline (equivalent to 10–20 μg l-adrenaline) produced ventricular fibrillation in cats. Although an accumulation of clinical evidence supported an equivalent danger, the results of these studies cannot be applied directly to man or other species; the dog heart, for example, is markedly less susceptible to ventricular arrhythmias (Embley, 1915; Stutzman and Pettinga, 1949). In dogs anaesthetized with chloroform, adrenaline 10 μg per kg, injected in less than one minute, failed to induce fibrillation (Meek et al., 1937).

A dose of adrenaline too small to induce ventricular tachycardia in normal unanaesthetized dogs was shown to do so with great regularity in the same animals under cyclopropane anaesthesia (Meek et al., 1937; Orth et al., 1939). Studies with trichloroethylene have yielded similar results (Waters et al., 1943; Barnes and Ives, 1944; Morris et al., 1953).

The mechanism of spontaneous or adrenaline-induced cardiac arrhythmias under anaesthesia is poorly understood. Levy believed that cardiac irregularities during chloroform anaesthesia were produced by sympathetic stimulation acting on a heart rendered irritable by the anaesthetic. Arrhythmias induced by adrenaline were apparently not directly associated with a rise in blood pressure. Similarly, in spite of conflicting evidence (Shen, 1938; Shen and Marri, 1940), the hypertension produced by adrenaline does not appear to be directly responsible for ventricular arrhythmias under cyclopropane anaesthesia (Allen et al., 1940).

Beattie et al. (1930), confirmed Levy's work and concluded from their own studies that a sensitizing hypothalamic centre was required for chloroform-induced extrasystoles. It has also been deduced that cyclopropane sensitizes the heart to adrenaline by direct stimulation of a centre above the pons (Allen et al., 1940). Afferent stimuli from the mesentery may also play a part (Stutzman et al., 1947; Stutzman and Pettinga, 1949). Cardiac sympathectomy abolishes the spontaneous arrhythmias produced by cyclopropane (Allen et al., 1945) but has a much smaller effect on adrenaline-induced ventricular arrhythmias under cyclopropane anaesthesia (Rennick et al., 1951).

Orth et al. (1939) showed that sensitization of the heart to cyclopropane was produced by primary or secondary catechol amines containing 2 hydroxyl groups, in the 3, 4 (meta, para) positions on the benzene ring. Ephedrine and phenylephrine, for example, did not affect cardiac rhythm in doses comparable to those of adrenaline and noradrenaline; excepting phenylephrine, all the pressor amines tested produced tachycardia. Phenylephrine appeared to be the safest drug for use with chloroform, ether, or cyclopropane.

The ease with which adrenaline produced ventricular fibrillation, from Levy's studies, subsequently led to the view that primary cardiac failure under chloroform anaesthesia could be induced by release of endogenous adrenaline, but there is no direct evidence for this in man. A possible role of endogenous adrenaline in spontaneous cyclopropane arrhythmias (Stutzman and Pettinga, 1949) also lacks supporting evidence.

It should be noted that the amount of adrenaline necessary to induce serious cardiac arrhythmias in laboratory animals is usually of the order of 10–20 μg per kg, which must lead to a precipitate increase in blood adrenaline concentration to levels almost certainly well outside the physiological range in man.

The protection against adrenaline-induced cardiac arrhythmias afforded by the adrenergic blocking agents is of value in the safe management of anaesthesia for the patient with a phaeochromocytoma. Dibenamine (Nickerson et al., 1946; Nickerson and Smith, 1949; Nickerson and Nomaguchi, 1949), the benzodioxane compounds (Dongen, 1939; Shen, 1938), the dihydrogenated ergot alkaloids (Orth and Ritchie, 1947), tolazoline (Nickerson and Smith, 1949), and phentolamine (Morris et al., 1952) all share this property, although they uniformly fail to antagonize the

positive chronotropic and inotropic cardiac effects of adrenaline (Nickerson, 1949). There appear to be at least two components in the protection provided by dibenamine against cyclopropane-adrenaline arrhythmias. There is a direct protection of the myocardium in doses greater than those required to reverse the pressor response to injected adrenaline. Another factor may be the avoidance of myocardial stress secondary to the rise in systemic arterial pressure which would occur in the absence of an adrenergic blocking agent (Nickerson and Nomaguchi, 1949).

REFERENCES

Acheson, G. H., and Moe, G. K. (1946). *J. Pharmacol.*, **87**, 220.

Ahlquist, R. P., Huggins, R. A., and Woodbury, R. A. (1947). *J. Pharmacol.*, **89**, 271.

Allen, C. R., Stutzman, J. W., and Meek, W. J. (1940). *Anesthesiology*, **1**, 158.

—— Hoeflich, E. A., Cooper, B. M., and Slocum, H. C. (1954). *Anesthesiology*, **6**, 261.

Allen, E. V., Bannon, W. G., Upson, M., Huizenga, K. A., Bastron, J. A., and Waugh, J. M. (1951). *Trans. Ass. Amer. Phys.*, **64**, 109.

Alwall, N., and Wulff, H. B. (1948). *Acta chir. scand.*, **96**, 337.

Anderson, W. H., Rolues, L. S., and Doerner, A. A. (1952). *Amer. J. Med.*, **43**, 252.

Apgar, V., and Papper, E. M. (1951). *Arch. Surg.* (Chicago), **62**, 634.

Axelrod, J., Aronow, L., and Brodie, B. B. (1952). *J. Pharmacol.*, **106**, 166.

Bacq, Z. M., and Fredericq, H. (1934). *C. R. Soc. Biol.* (Paris), **117**, 806.

Bainbridge, F. A., and Trevan, J. W. (1917). *Brit. med. J.*, **1**, 381.

Barcroft, H., and Konzett, H. (1949). *J. Physiol.* (Lond.), **110**, 194.

—— —— Swan, H. J. C. (1951). *J. Physiol.* (Lond.), **112**, 273.

—— Starr, I. (1951). *Clin. Sci.*, **10**, 295.

Barnes, C. G., and Ives, J. (1944). *Proc. roy. Soc. Med.*, **37**, 528.

Barnett, A. J., Blacket, R. B., Depoorter, A. E. Sanderson, P. H., and Wilson, G. M. (1950). *Clin. Sci.*, **9**, 151.

Bartels, E. C., and Cattell, R. B. (1950). *Ann. Surg.*, **131**, 903.

Bartorelli, C., Carpi, A., and Cavalca, L. (1954). *Brit. J. Pharmacol.*, **9**, 476.

Beattie, J., Brow, G. R., and Long, C. N. H. (1930). *Proc. Ass. Res. nerv. Dis.*, **9**, 249.

Beer, E., King, F. H., and Prinzmetal, M. (1937). *Ann. Surg.*, **106**, 85.

Bennett, L. L., and Fisher, C. W. (1948). *J. Pharmacol.*, **93**, 482.

Bhatia, B. B., and Burn, J. H. (1933). *J. Physiol.* (Lond.), **78**, 257.

Bing, R. J., and Thomas, C. B. (1945). *J. Pharmacol.*, **83**, 21.

Biskind, G. R., Meyer, M. A., and Beadner, S. A. (1941). *J. Clin. Endocr.*, **1**, 113.

Blacket, R. B., Pickering, G. W., and Wilson, G. M. (1950). *Clin. Sci.*, **9**, 247.

Blacklock, J. W. S., Ferguson, J. W., Mack, W. S., Shafar, J., and Symington, T. (1947). *Brit. J. Surg.*, **35**, 179.

Blalock, A. (1927). *Arch. Surg.* (Chicago), **14**, 732.

Bluntschli, H. J., and Goetz, R. H. (1948). *Amer. Heart J.*, **35**, 873.

Bovet, D., and Simon, A. (1937). *Arch. int. Pharmacodyn.*, **55**, 15.

Boyd, A. M. (1956). *Lancet*, **2**, 869.

Brace, D. E., Scherf, D., and Spire, L. J. (1941). *Anesthesiology*, **2**, 261.

Brewster, W. R., Bunker, J. P., and Beecher, H. K. (1952). *Amer. J. Physiol.*, **171**, 37.

—— Isaacs, J. P., and Wainø-Andersen, T. (1953). *Amer. J. Physiol.*, **175**, 399.

Bulbring, B. (1949). *Brit. J. Pharmacol.*, **4**, 234.

—— Burn, J. H. (1949). *Brit. J. Pharmacol.*, **4**, 245.

Cahill, G. F. (1948). *J. Amer. med. Ass.*, **138**, 180.

—— Aranow, H. (1949). *Ann. intern. Med.*, **31**, 389.

Calkins, E., Dana, G. W., Seed, J. C., and Howard, J. E. (1950). *J. clin. Endocr.*, **10**, 1.

Cattell, McK. (1923). *Arch. Surg.* (Chicago), **6**, 41.

Cleghorn, R. A., Fowler, J. L. A., Greenwood, W. F., and Clarke, A. P. W. (1950). *Amer. J. Physiol.*, **161**, 21.

Cobb, C. C., Hall, J., and Hall, R. A. (1953). *Lancet*, **1**, 973.

Console, A. D., Dunbar, H. S., and Ray, B. S. (1950). *Surgery*, **28**, 428.

Corbett, J. F. (1942). *J. Amer. med. Ass.*, **72**, 543.

Crawford, T. B. B., and Outschoorn, A. S. (1951). *Brit. J. Pharmacol.*, **6**, 8.

Dale, H. H. (1906). *J. Physiol.* (Lond.), **34**, 163.

—— (1933). *J. Physiol.* (Lond.), **80**, 10P.

DeCourcy, J. L., and DeCourcy, C. B. (1952). *Phaeochromocytoma and the General Practitioner.* Cincinnati: DeCourcy Clinic.

De Largy, C., Greenfield, A. D. M., McCorry, R. L., and Whelan, R. F. (1950). *Clin. Sci.*, **9**, 71.

DeVleeschhouwer, G. (1935). *Arch. int. Pharmacodyn.*, **50**, 251.

Dongen, K. van (1939). *Arch. int. Pharmacodyn.*, **63**, 88.

Drill, V. A. (1949). *New Engl. J. Med.*, **241**, 777.

Duff, R. V. (1956). *Brit. med. J.*, **2**, 857.

Dundee, J. W. (1956). *Thiopentone and other Thiobarbiturates*, Edinburgh: E. and S. Livingstone.

Eisleb, O. (1934). *Chem. Abstr.*, **28**, 2850.

Elliott, T. R. (1912). *J. Physiol.* (Lond.), **44**, 374.

Elmes, P. C., and Jefferson, A. A. (1942). *J. Physiol.* (Lond.), **101**, 355.

Embley, E. H. (1915). *Lancet*, **2**, 283.

Emlet, J. R., Gromson, K. S., Bell, D. M., and Orgain, E. S. (1951). *J. Amer. med. Ass.*, **146**, 1383.

Engel, A., and Euler, U. S. von (1950). *Lancet*, **2**, 387.

Erlanger, J., and Gasser, H. S. (1919). *Amer. J. Physiol.*, **49**, 345.

Euler, U. S. von (1949). *Acta. physiol. scand.*, **19**, 207.

—— (1951). *Ann. Surg.*, **134**, 929.

—— Hellner, S. (1951). *Acta physiol. scand.*, **22**, 161.

—— Floding, I. (1955a). *Acta physiol. scand.*, **33**, Supplement 118, 45.

—— —— (1955b). *Acta physiol. scand.*, **33**, Supplement 118, 57.

Euler, U. S. von, and Orwen, I. (1955). *Acta Physiol. scand.*, **33**, Supplement 118, 1.
Fellows, E. J., McLean, R. A., Macko, E., Kerwin, J. F., Hall, G. C., Milnes, F. J., Witt, I. H., and Ullyot, G. E. (1954). *J. Pharmacol.*, **110**, 463.
Fertig, H. H., Taylor, R. D., Corcoran, A. C., and Page, I. H. (1951). *Ann. intern. Med.*, **35**, 1358.
Fisher, C. W., Bennett, L. L., and Allahwala, A. (1951). *Anesthesiology*, **12**, 19.
Fourneau, E., and Bovet, D. (1933). *Arch. int. Pharmacodyn.*, **46**, 178.
Fränkel, F. (1886). *Virchows Arch. path. Anat.*, **103**, 244.
Freeman, N. E. (1933). *Amer. J. Physiol.*, **103**, 185.
—— Freedman, H., and Miller, C. C. (1941). *Amer. J. Physiol.*, **131**, 545.
Freis, E. D., Stanton, J. R., and Wilkins, R. W. (1948). *Amer. J. Med. Sci.*, **216**, 163.
Fritz, I., and Levine, R. (1951). *Amer. J. Physiol.*, **165**, 456.
Gaddum, J. H., and Lembeck, F. (1949). *Brit. J. Pharmacol.*, **4**, 401.
Gernandt, B. (1946). *Acta physiol. scand.*, **11**, Supplement, 35, 1.
Geschickter, C. F. (1935). *Amer. J. Cancer*, **23**, 104.
Gifford, R. W., Roth, G. M., and Kvale, W. F. (1952). *J. Amer. med. Ass.*, **149**, 1628.
Goldenberg, M. (1954). *Hypertension*, CIBA Foundation Symposium, p. 91.
—— Aranow, H. (1950). *J. Amer. med. Ass.*, **43**, 1139.
—— Rapport, M. M. (1951). *J. clin. Invest.*, **30**, 641.
—— Snyder, C. H., and Aranow, H. (1947). *J. Amer. med. Ass.*, **135**, 971.
—— Pines, K. L., Baldwin, E. deF., Green, D. G., and Roh, C. E. (1948). *Amer. J. Med.*, **5**, 792.
—— Faber, M., Alston, E. J., and Chargaff, E. (1949). *Science*, **109**, 534.
—— Serlin, J., Edwards, T., and Rapport, M. M. (1954). *Amer. J. Med.*, **16**, 310.
Goodall, A. L., and Symington, T. (1953). *Glasg. med. J.*, **152**, 97.
Gould, J., and Mindal, A. L. (1951). *Amer. Heart J.*, **42**, 460.
Graham, J. B. (1951). *Int. Abstr. Surg.*, **92**, 105.
Green, D. M. (1946). *J. Amer. med. Ass.*, **131**, 1260.
—— Johnson, A. D., Lobb, A., and Cusick, G. (1948). *J. Lab. clin. Med.*, **33**, 332.
—— Peterson, E. M. (1950). *J. Amer. med. Ass.*, **142**, 408.
Greenwald, H. P., Gootnick, A. Luger, N. M., and King, J. A. (1952). *New. Engl. J. Med.*, **246**, 252.
Guarneri, V., and Evans, J. A. (1948). *Amer. J. Med.*, **4**, 806.
Haimovici, H., Moser, M., and Krakauer, H. (1951). *Proc. soc. exp. Biol.* (N.Y.), **77**, 477.
Hamilton, W. F., Woodbury, R. A., and Vogt, E. (1939). *Amer. J. Physiol.*, **125**, 130.
Hammond, W. G., Aronow, L., Moore, F. D. (1956). *Ann. Surg.*, **144**, 715.
Handovsky, H. (1948). *Arch. int. Pharmacodyn.*, **75**, 449.
Harrison, B. L., and Seward, E. H. (1954). *Brit. med. J.*, **1**, 1077.
Harvey, S. C., and Nickerson, M. (1954). *J. Pharmacol.*, **112**, 274.
—— Wang, C. Y., and Nickerson, M. (1952). *J. Pharmacol.*, **104**, 363.
Hecht, H. H., and Anderson, R. B. (1947). *Amer. J. Med.*, **3**, 3.
—— Crandall, R., and Samuels, A. J. (1950). *Fed. Proc.*, **9**, 283.
Henderson, Y., Prince, A. L., and Haggard, H. W. (1917). *Amer. J. Physiol.*, **69**, 965.
Henle, J. (1865). *Z. rat. med.*, **24**, 142.
Henry, M. U. (1954). *Brit. med. J.*, **2**, 344.
Hermann, H., and Vial, J. (1942). *C. R. Soc. Biol.* (Paris), **136**, 803.
Herrold, E. A., Cameron, A., Earl, A., Roth, F., Smith, J., Smith, N., Sorensen, E., and Craver, B. N. (1949). *Fed. Proc.*, **8**, 302.
Heymans, C., and Bouckaert, J. J. (1935). *C. R. Soc. Biol.* (Paris), **120**, 79.
Holton, P. (1949). *Nature* (Lond.), **163**, 217.
Hubble, D. (1951). *Arch. Dis. Childh.*, **26**, 340.
Hunter, J. D., Bayliss, R. I. S., and Steinbeck, A. W. (1955). *Lancet*, **1**, 884.
Hyman, A., and Mencher, W. H. (1943). *J. Urol.* (Baltimore), **49**, 755.
James, W. O. (1948). *Nature* (Lond.), **161**, 851.
Johnson, S. R. (1949). *Anesthesiology*, **10**, 379.
Jourdan, F., and Galy, S. (1939). *C. R. Soc. Biol.*, (Paris), **131**, 1057.
Koehler, A. E., Marsh, N., and Hill, E. (1937). *J. biol. Chem.*, **119**, LIX.
Kohn, A. (1903). *Arch. Anat. micr.*, **62**, 263.
Kurland, G. S., and Freedberg, A. S. (1951). *Proc. Soc. exp. Biol.* (N.Y.), **78**, 28.
—— Malach, M. (1952). *New. Engl. J. Med.*, **247**, 283.
Labbé, M., Tinel, J., and Doumer (1922). *Bull. Soc. méd., Hôp. Paris*, **46**, 982.
LaDue, J. S., Murison, P. J., and Pack, G. T. (1948). *Ann. intern. Med.*, **29**, 914.
Lamson, P. D., and Keith, N. M. (1916). *J. Pharmacol.*, **8**, 247.
Levy, A. G. (1912). *Brit. Med. J.*, **2**, 627.
—— (1913). *Heart*, **4**, 319.
—— (1914). *Heart*, **5**, 299.
—— (1919). *Heart*, **7**, 105.
—— Lewis, T. (1912). *Heart*, **3**, 99.
Long, C. N. H., and Fry, E. G. (1945), *Proc. Soc. exp. Biol.* (N.Y.), **59**, 67.
Longino, F. H., Grimson, K. S., Chittum, J. R., and Metcalf, B. H. (1949). *Surgery*, **26**, 421.
Lund, A. (1950). *Acta Pharmacol.* (*Kbh.*), **6**, 137.
MacKeith, R. (1944). *Brit. Heart J.*, **6**, 1.
Manger, W. M., Flocks, E. V., Berkson, J., Bollman, J. L., Roth, G. M., Baldes, E. J., and Jacobs, M. (1954). *Circulation* (N.Y.), **10**, 641.
Masson, P., and Martin, J. F. (1923). *Bull. Ass. franç. Cancer*, **12**, 135.
Mayo, C. H. (1927). *J. Amer. med. Ass.*, **89**, 1047.
McGavack, T. H., Benjamin, J. W. Speer, F. D., and Klotz. S. (1942). *J. Clin. Endocr.*, **2**, 332.
Meek, W. J., Hathaway, H. R., and Orth, O. S. (1937). *J. Pharmacol.*, **61**, 240.
Meier, R., and Yonkman, F. F. (1949). *Fed. Proc.* **8**, 319.
—— —— Craver, B. N., and Gross, F. (1949). *Proc. Soc. exp. Biol.* (N.Y.), **71**, 70.
Millar, R. A. (1956). *J. Pharmacol* (in press).
Moe, G. K. (1948). *J. Amer. med. Ass.*, **137**, 1115.
Morison, R. S., and Lissak, K. (1938). *Amer. J. Physiol.*, **123**, 404.
Morris, L. E., Noltensheyer, M. H., and White, J. M. (1953). *Anesthesiology*, **14**, 153.

Morris, L. E., Yein, C. S., Haid, B., and White, J. M. (1952). *J. Pharmacol.*, **106**, 49.
Morrison, J. L., and Farrar, C. H. (1949). *Proc. Soc. exp. Biol.* (N.Y.), **71**, 235.
Moulton, R., and Willoughby, D. A. (1955). *Lancet*, **2**, 16.
Moyer, J. H., Huggins, R. A., and Handley, C. A. (1953). *J. Pharmacol.*, **108**, 240.
Nasmyth, P. A. (1950). *J. Physiol.* (Lond.), **110**, 294.
Neff, F. C., Tice, G. M., Walker, G. A., and Ockerblad, N. (1942). *J. clin. Endocr.*, **2**, 125.
Nickerson, M. (1949). *Pharmacol. Rev.*, **1**, 27.
—— Goodman, L. S. (1947). *J. Pharmacol.*, **89**, 167.
—— Nomaguchi, G. M. (1949). *J. Pharmacol.*, **95**, 1.
—— Smith, S. M. (1949). *Anesthesiology*, **10**, 562:
—— —— Goodman, L. S. (1946). *Fed. Proc.*, **5**, 195.
Olmsted, J. M. D., and Ogden, E. (1930). *Proc. Soc. exp. Biol.* (N.Y.), **27**, 725.
Orth, O. S., and Ritchie, G. (1947). *J. Pharmacol.*, **90**, 166.
—— Leigh, M. D., Mellish, C. H., and Stutzman, J. W. (1939). *J. Pharmacol.*, **67**, 1.
Page, I. H., and Taylor, R. D. (1947). *J. Amer. med. Ass.*, **135**, 348.
—— —— (1950). *Circulation* (N.Y.), **1**, 1233.
Peart, W. S. (1954). Hypertension, CIBA Foundation Symposium, p. 104.
Phillips, W. C., and Freeman, N. E. (1933). *Proc. Soc. exp. Biol* (N.Y.), **27**, 725.
Pincoffs, M. C. (1929). *Trans. Ass. Amer. Phys.*, **44**, 295.
Price, H. L., and Helrich, M. (1955). *J. Pharmacol.*, **115**, 206.
Prime, F. J., and Gray, T. C. (1952). *Brit. J. Anaesth.*, **24**, 101.
Prohaska, J. V., Harms, H. P., and Dragstedt, L. R. (1937). *Ann. Surg.*, **106**, 857.
Prunty, F. T. G., Swan, H. J. C., and Wilson, G. M. (1950). *Lancet*, **1**, 759.
Ramey, E. R., Goldstein, M. J., and Levine, R. (1951). *Amer. J. Physiol.*, **165**, 450.
Raab, W. (1948). *Ann. intern. Med.*, **28**, 1010.
—— Humphreys, R. J. (1946). *J. Pharmacol.*, **88**, 268.
—— —— Lepeschkin, E. (1950). *J. Clin. Invest.*, **29**, 1397.
—— Smithwick, R. H. (1949). *J. clin. Endocr.*, **9**, 782.
Rennick, B. R., Pardo, E. G., Gruhzit, C. C., and Moe, G. K. (1951). *J. Pharmacol.*, **101**, 176.
Richards, V., and Hatch, F. N. (1951). *Ann. Surg.*, **134**, 40.
Rosenblueth, A., and Cannon, B. (1933). *Amer. J. Physiol.*, **105**, 373.
—— Cannon, W. B. (1936). *Amer. J. Physiol.*, **116**, 414.
Roth, G. M., and Kvale, W. F. (1945). *Amer. J. med. Sci.*, **210**, 653.
Rothlin, E. (1925). *Klin. Wschr.*, **4**, 1437.
—— (1947). *Bull. schweiz. Akad. med. Wiss.*, **2**, 249.
Roux (1926). *Thèse, Lausanne.*
Schlossmann, H., and Mugge, H. (1929). *Arch. exp. Path. Pharmak.*, **144**, 133.
Shaw, F. H. (1938). *Biochem. J.*, **32**, 19.
Shen, T. C. R. (1938). *Arch. int. Pharmacodyn.*, **59**, 243.
—— Marri, R. (1940). *Arch. int. Pharmacodyn.*, **64**, 58.
Shepherd, D. M., and West, G. B. (1951). *Brit. J. Pharmacol.*, **6**, 665.
Shipley, A. M. (1929). *Ann. Surg.*, **90**, 742.
Smithwick, R. H. (1946). Personal communication to Goldenberg et al. (1947).
—— Greer, W. E. R., Robertson, C. W., and Wilkins, R. W. (1950). *New Engl. J. Med.*, **242**, 252.
Spatt, S. D., and Grayzel, D. M. (1948). *Amer. J. med. Sci.*, **216**, 39.
Spear, H. C., and Griswold, D. (1948). *New. Engl. J. Med.*, **239**, 736.
Strombeck, J. P., and Hedberg, T. P. (1939). *Acta. chir. scand.*, **82**, 177.
Stutzman, J. W., Murphy, Q., Allen, C. R., and Meek, W. J. (1947). *Anesthesiology*, **8**, 579.
—— Pettinga, F. L. (1949). *Anesthesiology*, **10**, 374.
Swan, H. J. C. (1949). *Lancet*, **2**, 508.
—— (1951). *Brit. med. J.*, **1**, 440.
Symington, T., and Goodall, A. L. (1953). *Glasg. med. J.*, **152**, 75.
Thompson, J. E., and Arrowood, J. G. (1954). *Anesthesiology*, **15**, 658.
Trapold, J. H., Warren, M. R., and Woodbury, R. A. (1950). *J. Pharmacol.*, **100**, 119.
Uricchio, J. F., Calenda, D. G., and Cutts, F. B. (1953). *J. Amer. med. Ass.*, **152**, 607.
Vaguez, H., Donzelot, E. (1926). *Presse méd.*, **34**, 1329.
Vogt, M. (1944). *J. Physiol.* (Lond.), **103**, 317.
—— (1945). *J. Physiol.* (Lond.), **104**, 60.
—— (1952). *J. Physiol.* (Lond.), **118**, 588.
—— (1955). *The Human Adrenal Cortex*, CIBA Foundation Symposium, p. 241.
Volhard, F. (1944). *Münch. med. Wschr.*, **91**, 120.
Wada, M., Fuzii, K., Sibuta, H., and Sakurai, H. (1940). *Tohoku J. exp. Med.*, **37**, 442.
Walton, J. N. (1950). *Lancet*, **1**, 438.
Ward, G. E. S., Riches, E. W., and Johnson, B. (1952). *Arch. Middx. Hosp.*, **2**, 133.
Warren, M. R., Woodbury, R. A., and Trapold, J. H. (1949). *Fed. Proc.*, **8**, 343.
Waters, R. M., Orth, O. S., and Gillespie, N. A. (1943). *Anesthesiology*, **4**, 1.
Watts, D. T. (1953). *J. Pharmacol.*, **114**, 203.
Weil-Malherbe, H. and Bone, A. D. (1953). *Lancet*, **1**, 974.
West, G. B. (1952). Personal communication to Goodall and Symington (1953).
—— Shepherd, D. M., Hunter, R B., and MacGregor, A. R. (1953). *Clin. Sci.*, **12**, 317.
Wilkins, R. W., Greer, W. E. R., Culbertson, J. W., Halperin, M. H., Litter, J., Burnett, C. H., and Smithwick, R. H. (1950). *Arch. intern. Med.*, **86**, 51.
Wood, P. (1950). *Diseases of the Heart and Circulation.* London: Eyre and Spottiswoode.
Woods, L. A., Wyngaarden, J. B., Rennick, B., and Seevers, M. H., (1949). *J. Pharmacol.*, **95**, 328.
Woods, E. F., Richardson, J. A., Richardson, A. K., and Bozeman, R. F. (1956). *J. Pharmacol.*, **116**, 351.
Wordsworth, V. P. (1955). *Brit. J. Anaesth.*, **27**, 535.
Young, H. H. (1936). *Surg. Gynec. Obstet.*, **63**, 174.
Yonkman, F. F., Stilwell, D., and Jeremias, R. (1944). *J. Pharmacol.*, **81**, 111.
Zweifach, B. W., Shorr, E., Baez, S., and Rosenfeld, S. J. (1947). *J. clin. Endocr.*, **7**, 460.

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SOME EFFECTS OF PREMEDICATION

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THE concept and practice of pre-anaesthetic medication were introduced by Claude Bernard (1869) and Labbe and Goujon (1872) who administered morphine before inducing anaesthesia with chloroform. A few years later Schäfer (1880) and Dastre and Morat (1884) recommended giving atropine as well as morphine. Scopolamine was first used by Schneiderlin (1903) and papaveretum (Omnopon) by Leipoldt (1911). Despite the wide variety of agents which have since been introduced, these four drugs in various combinations remain among the most commonly used.

The several desirable actions of these drugs are unfortunately accompanied by some disadvantageous ones, foremost among which is respiratory depression. Summation of this depression of breathing with that caused by the various hypnotics and analgesics employed in anaesthesia can produce a severe diminution of effective pulmonary ventilation with all its consequences.

There have been very few studies of the action of these premedicant combinations on the respiration and the results are inadequate and sometimes conflicting. Nevertheless the findings form the basis of our present knowledge of the respiratory effects of these drugs and are authoritatively quoted in textbooks of pharmacology. The present investigation was undertaken to assess and compare the respiratory and other effects of the four combinations: morphine + atropine; morphine + scopolamine; papaveretum + atropine; and papaveretum + scopolamine; each given in a fixed dose per body weight under standard conditions.

Material and Method.

The four drug combinations were given each to 50 patients on a completely unselected basis. The investigation was confined to subjects aged 20–60 years (inclusive); all were in good general condition. While it might have been more in line with clinical practice to have given the drugs by subcutaneous injection, the inequalities of depth of injection, rate of absorption, and difficulty of assuring that in all cases measurements would be made at the same time interval after administration decided in favour of the intravenous route.

The work has consisted of the measurement of pulse, blood pressure and respiratory changes, and the recording of general effects following injection of these premedication drugs. When the study was originally planned we intended to compare the hypnotic and sedative efficacy of the drug combinations. Several methods of estimating these functions were tried but none proved satisfactory under the limiting conditions of the work. This aspect of the drugs' actions was therefore excluded from the investigation. The observations were made in the anaesthetic room on patients who were about to undergo operation. The subjects breathed room air throughout. The respiratory volume was measured with a Bennett respiration meter. This meter has a very small dead space and, under the present conditions, the resistance is less than 0.25 cm H_2O; it permits measurement to the nearest 25 ml. Serial blood pressure readings could not be taken in every case but only when skilled help was available.

The age, sex and weight distributions of the 200 patients are shown in table I. The drug dosage used throughout was: morphine 1/6 mg/kg; atropine 1/100 mg/kg; papaveretum 1/3 mg/kg; scopolamine 1/150 mg/kg.

TABLE I
Age, sex and weight of patients

	M+A	M+S	P+A	P+S	All
Mean age (yrs.)	41.4	43.5	44.6	42.5	43.0
Mean wt. (lb)	147.1	143.0	144.3	138.5	143.2
Max. wt. (lb)	211	218	218	182	218
Min. wt. (lb)	87	93	94	99	87
No. of males	28	31	20	31	110
No. of females	22	19	30	19	90

(1 lb = 0.45 kg)

EXPERIMENTAL TECHNIQUE

Control readings were first made; the resting pulse rate and blood pressure were taken and the rate and volume of breathing measured over a period of 1 minute. The premedication was then injected into an arm vein, a stopwatch being started at the commencement of the injection which took 10–15 seconds. The patient was asked to report any symptom or sensation immediately; no leading questions were asked. Readings of pulse, blood pressure, respiration rate and volume were made at the 3rd, 5th, 7th and 9th minutes after injection. The pressure of work in the theatre made it necessary that the patient should not be retained unduly. Therefore, as the previous work suggested that the maximum respiratory depression would have been reached by 10 minutes, the duration of the tests was limited to this time. (In a few cases the 9-minute reading had to be forgone, see table II.) At each reading the patient usually reproduced what he considered to be normal breathing. A note was made of restlessness, pruritus, wealing, etc.

RESULTS

Subjective Symptoms.

Following injection of the drugs there was an interval of 10–30 seconds before symptoms were reported. The patient's account of his sensations was largely influenced by his descriptive ability and also by the speed of his reporting. This has rendered difficult an analysis of the symptoms, for the same sensation has undoubtedly been given different names by different patients.

The symptoms frequently started in one or other arm and proceeded to the legs and/or body and/or head. Certain sensations were very common: numbness, tingling, warmth, pain, and "tightness". Other symptoms which were complained of less commonly were dizziness, palpitations, and sensations (such as fullness) in the head. A few patients complained of dryness, difficulty in breathing, "shakiness" or throbbing. Six patients denied any symptoms. Not infrequently there was a sequence of sensations starting with tightness or aching followed by heaviness, warmth, numbness, throbbing or burning, or by a few of these symptoms. Sixty-four patients reported drowsiness either spontaneously or on indirect questioning.

There was no significant difference between the incidence of these various symptoms with the four drug combinations. Almost every patient developed some flushing of the face within a few minutes of receiving his injection.

Wealing.

Linear wealing along the course of the injected vein, and sometimes its connections, occurred in 34 of the 200 patients. There was no significant difference of incidence between the four groups. The symptoms in these subjects did not differ from those of the other patients and there was no evidence of general hypersensitivity; one of these patients had no symptoms at all. Only one patient had an exaggerated general response to the premedicant drug; he did not exhibit any wealing.

Circulatory Changes.

There was no constant change in the blood pressure in the first 10 minutes after intravenous premedication with any of the four pairs of drugs. Most commonly the blood pressure did not change at all; sometimes there was a temporary rise and less often a transient fall in pressure.

The pulse showed a marked acceleration in rate in most cases (table II). The peak rate was evident at the 3rd minute and was in the order of 20–30 per cent above the control figures. From then onward there was a gradual fall but at the end of 10 minutes the rate was still 17–24 per cent above the pre-injection level. Combinations with atropine gave a significantly faster pulse than scopolamine combinations except that M+A was similar to M+S.

Respiratory Changes.

Rate. The drug combinations had little effect on the respiration rate (table III). There was no

TABLE II
Pulse changes

Series		Control	3 minutes	5 minutes	7 minutes	9 minutes
M + A	No. of patients	50	50	50	50	21
	Mean	86.52	110.48	109.12	107.95	103.33
	S.E. ±	2.07	2.33	2.15	2.41	4.56
M + S	No. of patients	50	50	50	50	35
	Mean	86.64	106.24	103.55	101.84	100.97
	S.E. ±	1.98	2.70	2.63	2.66	3.24
P + A	No. of patients	50	50	50	50	36
	Mean	89.76	116.48	115.46	114.58	111.52
	S.E. ±	1.77	2.64	2.78	2.81	3.71
P + S	No. of patients	50	50	50	50	33
	Mean	85.60	102.52	99.13	98.08	99.8
	S.E. ±	1.99	2.33	2.49	2.48	3.39

A statistical analysis of the data has been carried out by Miss M. H. Russell, Medical Statistician to the Christie Cancer Hospital, Manchester. The minimal level of significance has throughout been taken as $P<0.05$. All the mean control values in all series were found to be statistically homogeneous. It was considered likely that the smaller number of cases at 9 minutes accounted for the diminished level of significance in comparisons at that time interval.

TABLE III
Respiratory rate changes

Series	Control	3 minutes	5 minutes	7 minutes	9 minutes
M + A	17.4	16.6	16.7	16.8	15.5
S.E. ±	0.6	0.7	0.7	0.8	0.9
M + S	17.5	18.1	18.4	18.0	17.3
S.E. ±	0.5	0.7	0.7	0.6	0.6
P + A	17.5	16.5	17.0	17.0	16.7
S.E. ±	0.6	0.6	0.6	0.6	0.7
P + S	16.6	16.6	17.3	17.1	16.2
S.E. ±	0.5	0.5	0.6	0.6	0.6

significant difference between the experimental readings after the various combinations at any time interval.

Minute Volume. The minute volume showed a marked fall with all four drug mixtures (table IV). The fall occurred chiefly in the first 3 minutes but the volume continued to decline, although more gradually, throughout the first 10 minutes after administration.

Drug combinations containing papaveretum were more depressant to the respiration than those containing morphine. Comparing M + A with P + A and with P + S the morphine combination is significantly less depressant at most time intervals. Comparing M + S with P + A and with P + S the morphine combination is significantly less depressant at most time intervals. There appears to be no difference between the effects exerted by atropine and scopolamine.

Tidal Volume. As would be expected from the rate and minute volume changes there was a fall in tidal volume in all four series. The smallest deviation from the control volumes was after morphine + atropine and the greatest depression was caused by papaveretum + scopolamine (table V). These changes will, of course, be reflected in the effective ventilation. There was no significant difference between the effects of atropine and scopolamine at the level of significance adopted in this work (i.e. $P<0.05$). However, comparison of M + A and M + S suggests that the latter may be the more depressant, for there is a significant difference at the 7 per cent level at some time intervals.

TABLE IV
Minute Volume Changes

Series		Control	3 minutes	5 minutes	7 minutes	9 minutes
M + A	Mean minute volume (ml)	6567	5776	5445	5445	4971
	S.E. ±	268.5	252.1	231.6	219.2	318.2
M + S	Mean minute volume (ml)	6647	5911	5714	5326	5318
	S.E. ±	224.4	235.9	175.8	167.8	147.6
P + A	Mean minute volume (ml)	6086	5055	4983	4849	4827
	S.E. ±	204.6	234.4	201.3	192.1	206.8
P + S	Mean minute volume (ml)	6085	4781	4760	4624	4409
	S.E. ±	262.9	233.8	276.6	239.9	248.4

TABLE V
Tidal Volume Changes

	Control	3 minutes		5 minutes		7 minutes		9 minutes	
Series	Mean T.V. (ml)	Mean T.V. (ml)	% change T.V.	Mean T.V. (ml)	% change T.V.	Mean T.V. (ml)	% change T.V.	Mean T.V. (ml.)	% change T.V.
M + A	391	373	−4.5	346	−11.3	344	−12.0	354	−9.6
M + S	391	339	−13.3	324	−17.1	304	−22.2	318	−18.6
P + A	361	321	−11.2	305	−15.5	300	−17.1	301	−16.8
P + S	378	299	−21.0	288	−23.8	282	−25.3	276	−27.0

DISCUSSION

It is evident that the drug combinations investigated produce a marked respiratory depression in clinical dosage. The effect on the respiration of the individual drugs has been investigated by several workers but the combinations, as used in clinical practice, have been very inadequately studied. No previous investigation of the papaveretum combinations has been discovered.

Waters (1938) administered 16 mg morphine with either 0.64 mg scopolamine or 1.28 mg atropine to 10 adult male volunteers. Half-hourly readings were taken before and for 7 hours after hypodermic injection. He found that the atropine combination caused the greater depression of respiratory minute volume and that neither mixture had much effect on the respiratory rate. Wangeman and Hawk (1942) administered the same two drug combinations in the same dosages hypodermically to 5 trained volunteers and took readings at 15-minute intervals for 1½ hours. They found that morphine + atropine caused a marked early rise in pulse rate, a variable effect on the blood pressure, respiration rate and tidal volume, and a depression of the minute volume. Morphine + scopolamine caused an inconstant change in pulse rate and blood pressure, some decrease in respiratory rate and a slight decrease in minute volume. Adriani (1954) states that morphine and atropine, given in a ratio of 25 : 1, cause " a moderate decrease " in minute volume and some elevation of pulse rate. Morphine and scopolamine in 25 : 1 ratio are stated to cause a slight decrease in minute volume and no change in heart rate.

It will be seen that the present results are at variance with some of the previous findings. However, the other workers used very small series of cases, the dosages were different from the present ones, and the drugs were not administered on a dose per weight basis. The large individual variation in respiratory response to these drugs must also be borne in mind.

Ideally in an investigation of premedicant drugs the route of administration should be that commonly used in clinical practice. Although, for experimental expedience, the intravenous route was used here there is evidence to show that the present findings, both absolute and relative, are directly related to clinical practice. Thus Dripps and Comroe (1945) have shown that " the maximum respiratory depression following morphine is approximately the same whether the morphine be administered intravenously or intramuscularly ", and Adriani (1954) considers that the effect of these drug combinations 10 minutes after intravenous administration is the same as that 1½ hours after subcutaneous injection.

The use of the intravenous route for premedication will, of course, deny the patient the benefits of pre-operative sedation and cannot, therefore, be advocated for general use. However, occasions will arise when this route has to be used, as in an emergency, in the shocked patient, when premedication has been overlooked, or to supplement an inadequate or badly timed dose (Foldes and Swerdlow, 1954). Intravenous administration does ensure rapid action and absorption regardless of circulatory efficiency and has the further advantage that the full effect can be seen before anaesthesia is commenced. A disadvantage, an impression noted in the present work, is that patients tend to sleep longer postoperatively than after conventional hypodermic premedication. If thiopentone is to be used following intravenous premedication the dose should be reduced to avoid severe respiratory depression (Swerdlow, 1957).

The present investigation shows unequivocally that in clinical dosage combinations with morphine will cause significantly less depression of the respiration than papaveretum mixtures. From the point of view of respiratory depression alone there is a suggestion that atropine might be preferable to scopolamine for combination with morphine. However, Orkin and his colleagues (1956), Wangeman and Hawk (1942) and others accord to scopolamine a much greater drying effect and psychic depression than atropine. Taking into account also the amnesic properties of scopolamine and its lesser effect on the heart rate the balance might be inclined in its favour except at the extremes of age where its use is commonly avoided.

SUMMARY

Morphine and papaveretum, in combinations with atropine and scopolamine, have been administered intravenously in fixed dose per body weight to 200 patients. Changes in pulse, blood pressure, respiration rate and depth were recorded at intervals up to 10 minutes after injection and general effects noted.

The blood pressure showed no constant change. A rise in pulse rate occurred after all combinations and was generally greater after atropine mixtures. The respiration rate showed no significant change. The respiratory volume was diminished by all drug combinations, papaveretum causing a significantly greater depression than morphine.

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REFERENCES

Adriani, J. (1954). *The Pharmacology of Anaesthetic Drugs*, 3rd ed., Illinois, U.S.A.: Thomas.

Bernard, C. (1869). The combined action of morphia and Chloroform. *Lancet*, **2**, 789.

Dastre, A., and Morat, J. P. (1884). *Recherches Experimentales sur le Systeme Nerveuse Vasomoteur.* Paris: Masson.

Dripps, R. D., and Comroe, J. H. (1945). Clinical studies on morphine. *Anesthesiology*, **6**, 462.

Foldes, F. F., and Swerdlow, M. (1954). The use and abuse of anaesthetic drugs. *Penn. med. J.*, **57**, 1160.

Labbe, L., and Goujon, E. (1872). Sur l'action combinée de la morphine et du chloroforme. *Gaz. Hôp. (Paris)*, **45**, 251.

Leipoldt, C. L. (1911). Some remarks on pantopon anaesthesia. *Lancet*, **1**, 368.

Orkin, L. R., Bergman, P. S., and Nathanson, M. (1956). Effect of Atropine, Scopolamine and Meperidine on Man. *Anesthesiology*, **17**, 30.

Schäfer, E. A. (1880). Atropine as a preventive against the cardio-inhibitory effects of chloroform. *Brit. med. J.*, **2**, 620.

Schneiderlin, . (1903). Die Skopolamin (Hyoszin)-Morphium-narkose. *Münch. med. Wschr.*, **50**, 371.

Swerdlow, M. (1957). Respiratory Effects of Anaesthetics. *Anaesthesia* **12**, 42.

Wangeman, C. P., and Hawk, M. H. (1942). The effects of morphine, atropine and scopolamine on human subjects. *Anesthesiology*, **3**, 24.

Waters, R. M. (1938). A study of morphine, scopolamine and their relation to preoperative medication and pain relief. *Tex. St. J. med.*, **34**, 304.

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THE INVESTIGATION OF A SHORT-ACTING BARBITURATE, ILLUSTRATING THE FALLACIES OF CLINICAL IMPRESSIONS

BY

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WEESE and Koss (1954) reintroduced sodium 5-allyl-5-isobutyl thiobarbiturate (buthalitone sodium) as an ultra-short-acting barbiturate. They suggested that it was shorter acting than thiopentone and recommended it for operations in ambulatory patients lasting ten minutes or less. The patient, they claimed, was able to leave hospital within half an hour of his operation. This led me to suppose that this drug might be suitable for outpatient anaesthesia.

Preliminary trial in unpremedicated ambulatory patients showed that buthalitone (50 mg/stone (6.4 kg) of body weight), if injected rapidly, provided a brief period of unconsciousness ($\frac{1}{2}$–2 minutes) in healthy individuals of average build, and that this dosage corresponded roughly to 25 mg/stone of thiopentone given to obtain the same results.

CLINICAL TRIAL

The drug was given to 53 fit patients whose ages ranged from 5 to 60 years; there was no premedication used and the operations lasted from 15 to 120 seconds. The cases consisted of 35 outpatient incisions, 12 dental extractions, 3 minor e.n.t. operations and 3 manipulations. A dosage of 50 mg/stone of body weight was given to all patients of average build; it was increased slightly in the young and lean types and decreased in the elderly and fat. The drug was administered intravenously as a 10 per cent solution injected as rapidly as possible.

RESULTS

Operating Conditions.

These were classified as:

"Very good" where there was no response to stimulation.

"Good" where there was a slight response which did not require restraint.

"Fair" where there was reflex response which needed restraint.

"Bad" where the operation could not be performed without supplementary anaesthesia.

Very good	Good	Fair	Bad
14	19	13	7

A few (6) of the patients in the last two groups might have been classified as "Good" for the first 30 seconds of the operating time.

Duration.

This may be divided arbitrarily into three stages:

(1) The unconscious period, which lasted from 1 to 7 minutes (average 4 minutes).

(2) The immediate recovery period, when reorientation had taken place and animation was returning at a detectable rate. This usually lasted for 5–10 minutes.

(3) The delayed recovery or "hangover" period, when the rate of recovery was insidious. This lasted for some hours. The symptoms, though mild, were described as sleepy, "tight", euphoric or dopey. Nystagmus was noted in most patients during the first 30 minutes of this period.

Cardiovascular System and Respiratory System.

The drug did not appear to have a marked effect on blood pressure as detected by palpation at the wrist. Tachycardia of short duration was noted in seven of the first 25 cases after giving the injection.

A period of apnoea of from 2 to 5 seconds

followed the injection in most patients, but 10 seconds was the longest period of apnoea recorded. This contrasts strongly with the longer periods of apnoea which occur after the rapid injection of half the dosage of thiopentone.

Coughing, sneezing or retching as described by Ruddell (1956) was not observed in any of these patients. Retrograde amnesia was not a noticeable feature—in fact many of the patients on awakening had a complete continuity of thought and were very surprised that the operation had been completed.

Nausea and vomiting occured in one patient.

Children tended to be restless and irritable for some time after the operation.

The impressions gained from this clinical trial were that buthalitone was pleasant, relatively safe for the fit patient and that there was a rapid recovery of consciousness. The initial recovery period was rapid, but the mild "hangover" period persisted for some hours. Good operating conditions could be obtained in the majority of patients with buthalitone alone, and as there was only a short period of apnoea, supplementary inhalational anaesthesia could easily be introduced. It was therefore thought that buthalitone had many advantages over the existing barbiturates for short operations and that more objective measurements of these impressions should be carried out.

EFFECT ON BLOOD PRESSURE

Buthalitone as a 10 per cent solution was injected intravenously as rapidly as possible into two healthy volunteers in a dosage of 50 mg/stone (6.4 kg) of body weight, while the blood pressure was recorded from the brachial artery by means of a capacitance manometer (fig. 1).

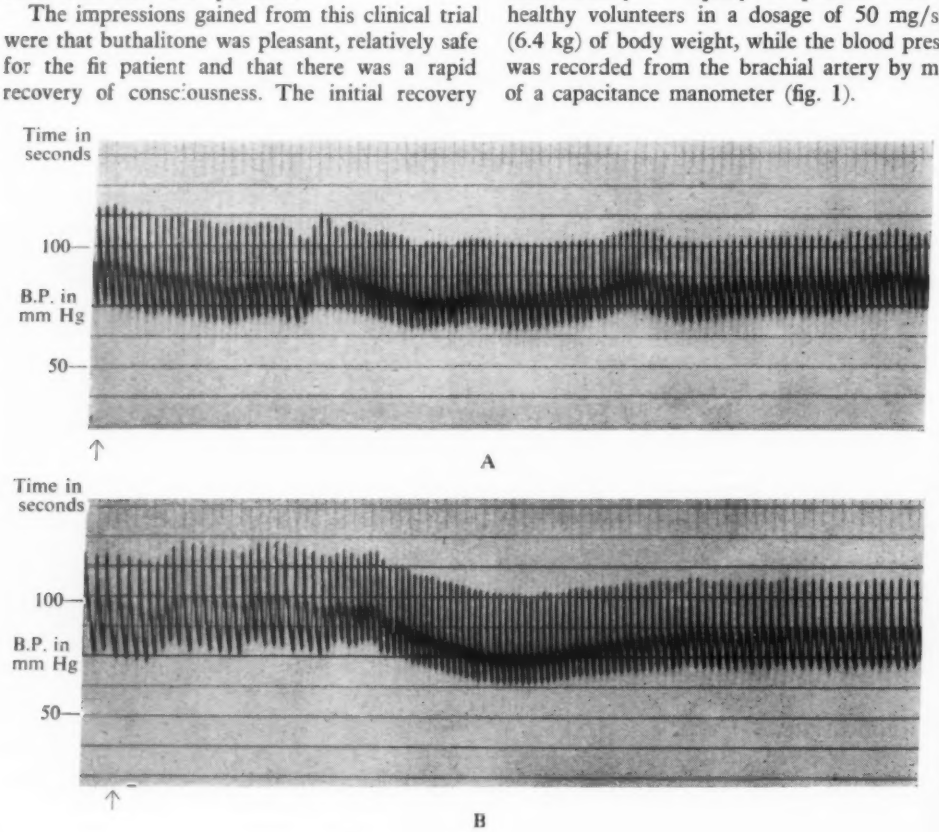

FIG. 1

Intra-arterial blood pressure records. The arrow indicates the point at which the drug was given.

From these records it is seen in A that there is a slight increase in pulse rate and very little drop in blood pressure, and in B that there is a reasonable drop in blood pressure and a marked acceleration of the heart occurs.

ELECTROENCEPHALOGRAPHY

Three volunteers were given buthalitone in the dosage and manner already described, while electroencephalographic tracings were taken. Consciousness was lost in about 30 seconds and e.e.g. pattern I (Kiersey et al., 1951) appeared rather abruptly, and was maintained for the next 1 to 3 minutes, when it gradually reverted to a more normal appearance. Even after 30 minutes, however, some fast activity of barbiturate sedation persisted. Figure 2 illustrates the average depth attained and the recovery of these three volunteers. Thiopentone 25 mg/stone of body weight was also given to these three volunteers as a control, and it was found that a much deeper level of anaesthesia was attained for a short period after the injection and that the initial recovery appeared to be more rapid (fig. 2).

The typical electroencephalographic patterns are easy to recognize; but as one pattern gradually merges into the next the intermediate points are difficult to position accurately. These points were plotted as accurately as possible (arbitrarily) for thiopentone in each subject, and a curve drawn.

The buthalitone pattern at a given moment was matched against the thiopentone tracing for the same subject and thus its position on the curve ascertained. Thus, if there was any inaccuracy in the thiopentone curve, the same mistake is transferred to the buthalitone curve (i.e. strict comparison).

It will be seen that there is a subdivision below pattern I where the subject is conscious but the

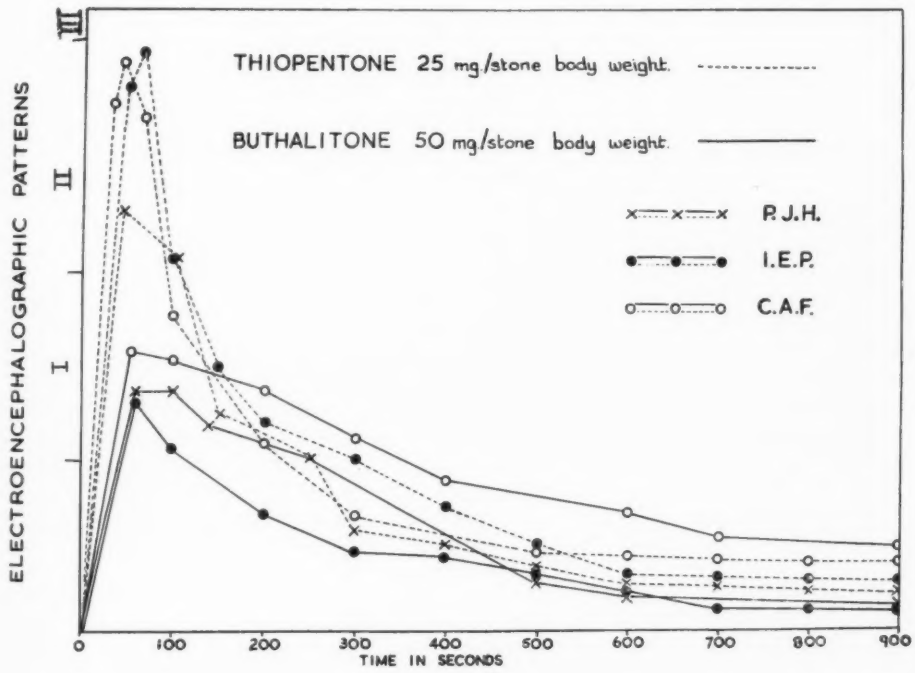

FIG. 2

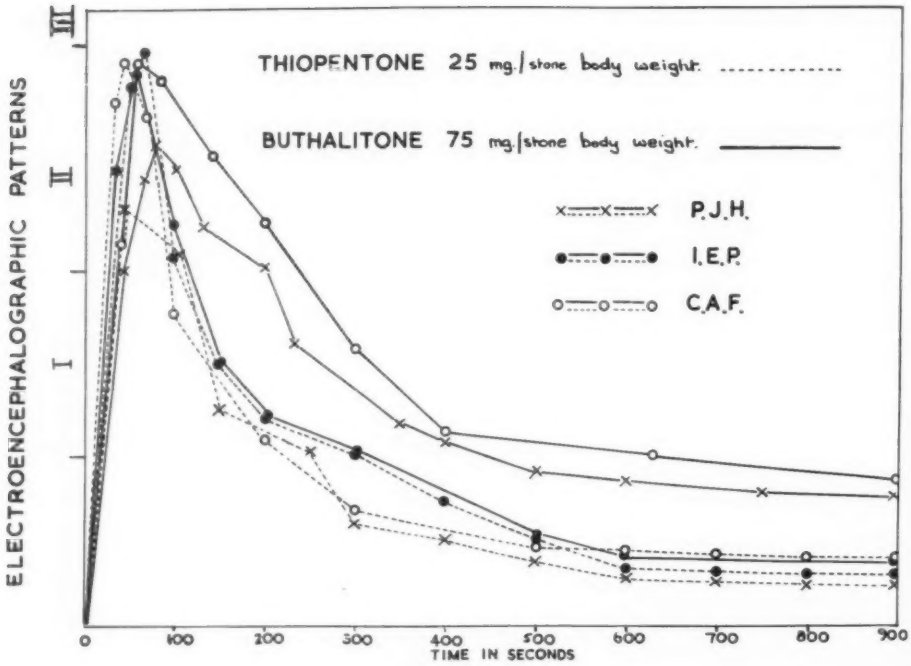

FIG. 3

electroencephalographic pattern has not returned to normal.

In this light level of sedation it was found that the occipital leads were most helpful in determining the position of the point on the curve. Alpha rhythm began to appear about halfway down this column and it became more prominent as it approached the base line.

The clinical findings bore a fairly direct relationship to the e.e.g. findings and agreed with those of Kiersey et al. (1951). In light pattern III and pattern II there is no response to painful stimulation and the eyelash reflex is absent. In pattern I reflex activity is returning but very sluggish at first. The eyelash reflex reappears and response to commands returns towards the lower levels of pattern I. Between pattern I and the normal rhythm there is a fast, spiky activity of barbiturate sedation during which time the patient feels sleepy and euphoric. Nystagmus was present during this period.

From these electroencephalographic studies it is evident that our clinical impressions of the relative potencies of these drugs were very misleading. The thiopentone group of patients went to a far deeper level of anaesthesia than the buthalitone group. This persisted for a brief period, when there was a rapid recovery to pattern I and thereafter a slower recovery of consciousness.

As regards the duration of sleep, our relative dosage of the two drugs was reasonably accurate but it gave to buthalitone an unwarranted advantage of having less of a hangover at any given period after the return of consciousness. The greater depth attained with thiopentone would presumably account for the more prolonged apnoea which occurred when this drug was given, as opposed to buthalitone. When the dosage of buthalitone was stepped up to give a comparable depth of anaesthesia to that produced by thiopentone, it became apparent that the recovery time is not as short as that of thiopentone (fig. 3).

SUMMARY AND CONCLUSIONS

A clinical trial of buthalitone on 53 fit unpremedicated patients is reported. Electroencephalographic recordings were made during induction and recovery from anaesthesia with this drug, and these are compared with those of thiopentone. The difficulty of interpreting the atypical electroencephalographic patterns is indicated and a comparative method of assessing depth, to overcome this difficulty, is described. Intra-arterial blood pressure was recorded on two volunteers. It is suggested that buthalitone has no advantages over thiopentone as a short-acting anaesthetic agent.

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REFERENCES

Kiersey, D. K., Bickford, R. G., and Faulconer, A., jr. (1951). E.C.G. Patterns Produced by Thiopental Sodium during Surgical Operations. *Brit. J. Anaesth.*, **23**, 141.

Ruddell, J. S. (1955). New Short-Acting Thiobarbiturate. *Lancet*, **2**, 1296.

Weese, H., and Koss, F. H. (1954). *Dtsch. med. Wschr.*, **79**, 601.

ROYAL SOCIETY OF MEDICINE: SECTION OF ANAESTHETICS

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The Anaesthetic Section of the Royal Society of Medicine is able to offer a Prize of £30 for the best paper submitted by medical practitioners of Senior Registrar or Registrar grading in the National Health Service holding a clinical appointment in an anaesthetic department or hospital. Fellowship of the Royal Society of Medicine is not necessary for entry.

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CYCLOPROPANE ANAESTHESIA: A TECHNIQUE SUITABLE FOR INFANTS

BY

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THE types of anaesthesia suitable for adults are not altogether suitable for infants, i.e. children under 2 years of age.

Venepuncture is often difficult and muscle relaxants are not always required; anoxia, associated with induction by nitrous oxide, is badly tolerated; tachypnoea may occur when trichloroethylene is used.

During ether anaesthesia excessive ventilation over long periods and circulatory depression in the deeper planes limit the operating time and predispose towards shock. It was dissatisfaction with ether, especially its adverse metabolic effects on feeble infants and those suffering from toxaemia, that led to this investigation of the use of cyclopropane.

Cyclopropane may be used in anaesthesia for infants by the to-and-fro carbon dioxide absorption technique (closed method) or by the partial rebreathing technique without carbon dioxide absorption (semiclosed method) or by a combination of these techniques.

Closed Method.

This technique is criticized by a number of authors on the following grounds:

(1) The resistance of the soda lime taxes the energy of the infant (Stephen, 1952).

(2) It is necessary to change the soda lime canisters at frequent and often inopportune moments (Bergner and Schafer, 1956).

(3) Icing of the canisters is often not sufficient to prevent a rise of body temperature during operation (Hampton et al., 1952).

(4) A serious carbon dioxide accumulation may be masked (Wilton, 1952).

(5) Excessive bleeding occurs (Wilton, 1952; Fairlie, 1954).

(6) Postoperative shock is more marked (Fairlie, 1954).

(7) Muscular relaxation is obtained only in deep planes of anaesthesia (Stephen, 1952).

Leigh and Belton (1950) consider that the "use of absorption technique in the first months of life is impracticable". Another important criticism of the closed method is that the proportions of the gases (cyclopropane, oxygen, carbon dioxide and water vapour) delivered to the patient's lungs are not known and there is a resultant danger of respiratory depression, serious cardiac irregularities and postoperative cyclopropane shock. This criticism also applies to the combination of closed and semiclosed methods, especially when nitrous oxide is used as well as cyclopropane and oxygen.

Semiclosed Method.

Cyclopropane has been used in this way:

(*a*) For the induction of ether anaesthesia (Deming, 1952; Zindler and Deming, 1953; Bergner and Schafer, 1956).

TABLE I

Flow rates					
Litres per minute			Ml per min	Approximate % of gases	
Total	Oxygen	Nitrous oxide	Cyclopropane	Cyclopropane	Oxygen
4¾	1¼	3	500	10	25
5	1¼	3	750	15	25
4	1¼	2	750	20	25

TABLE II

No. of cases anaesthetized	Range of ages	Operation	Duration of longer operations
NEONATAL			
1	6 hours	Meconium peritonitis volvulus, atresia and perforation of small intestine.	
1	15 hours	Exomphalos (infant of 3 lb weight).	
1	15 hours	Volvulus and perforation of small intestine.	2 hours
	8 days	Ileostolmy.	1 hour
1	3 days	Meconium ileus with fibrocystic pancreas.	
1	4 days	Hirschsprung's disease. Caecostomy.	
1	5 days	Laparotomy.	
1	7 days	Duodenal atresia.	1 hour
1	8 days	Coccygeal teratoma.	1 hour
1	8 days	Diaphragmatic hernia.	1 hour
INFANTS			
Abdominal			
1	5 weeks	Dilation of oesophageal stricture.	
3	5 weeks to 3 months	Pyloric stenosis.	
1	6 weeks	Umbilical hernia.	
1	8 weeks	Intestinal obstruction.	2¼ hours
1	9 weeks	Nephrectomy.	
3	4 months	Intussusception.	
1	6 months	Wilm's tumour.	1 hour
2	1 year	Inguinal hernia.	
1	2¼ years	Strangulated inguinal hernia.	
1	2¼ years	Pelvic peritonitis.	
1	2¼ years	Ruptured abdomen after operation for malrotation of gut.	
Plastic			
3	5 days to 2½ years	Circumcision.	
1	1 month	Tongue tie.	
6	5 months to 1½ years	Cleft lips and palates (Stages 1 and 2).	Up to 2 hours
1	9 months	Repair of separated pubis and urethra.	1½ hours
1	1¼ years	Repair of urethra.	
Orthopaedic			
4	1½ to 3½ years	Fractures and dislocations.	
1		Depressed fracture of skull. Removal of fragments.	
E.N.T.			
1	1 year	Mastoidectomy.	
Eye			
1	1 year	Enucleation of eyeball.	
14	6 weeks to 2 years	Examination of fundi, probing of tear ducts, chalazions, etc.	
Minor surgical			
26	18 days to 3½ years	Burns, abscesses, lacerations, bougies, etc.	

(*b*) As an adjuvant to nitrous oxide-oxygen anaesthesia, in 5 to 10 per cent concentrations, to produce analgesia in infants under 6 months old (Stephen and Slater, 1950; Stephen, 1954).

Combined Method.

The use of cyclopropane in a Heidbrink machine with circle absorption and open expiratory valve is described by Shane and Ashman (1952).

The following method of cyclopropane anaesthesia by the semiclosed technique has been tried over a period of about nine months on an unselected series of 84 cases (table II) and has been found to be both safe and suitable for operations on infants of up to two hours or more duration. It may be used on slightly older children for operations of short duration.

TECHNIQUE

Premedication. Atropine 0.15 mg up to 6 months old; 0.3 mg from 6 months to 2 years.

Atropine alone is used to avoid respiratory depression and to inhibit the secretions stimulated by cyclopropane. It also gives protection against vagal reflexes.

Induction. A Boyle's machine and Magill's rebreathing attachment or Cope's apparatus without the soda lime absorber are used, care being taken to ensure that the expiratory valve is opening easily. The oxygen flow rate is set at 1.25 litres per minute and normally remains at that setting throughout the operation.

The nitrous oxide flow is adjusted to 3 litres per minute. The mask, with expiratory valve fully open, is approximated gradually to the infant's face. Cyclopropane is added immediately the mask is in place and the flow steadily increased to 750 ml per minute to give a concentration of 15 per cent cyclopropane.

If a deeper level of anaesthesia is required the nitrous oxide flow rate is reduced to 2 litres per minute to give a concentration of about 20 per cent cyclopropane. The oxygen percentage may be increased at any time at the expense of the nitrous oxide, as for example for neonatal anaesthesia where the oxygen concentration should be at least 50 per cent for all operations of more than short duration. Intubation, facilitated by the relaxation of the masseters, is a protection against inhalation of stomach contents and laryngeal spasm which may occur at such light levels of anaesthesia.

Maintenance. A satisfactory level of anaesthesia for most operations is attained at about a 15 per cent concentration of cyclopropane. At 10 per cent limb movements are usually just abolished and the upper level of stage 3 plane 1 is attained. At 15 per cent lower plane 1 is reached and upper plane 2 at 20 per cent, although there is, of course, some individual variation.

With the flow rates recommended it is impossible, in the presence of an unobstructed airway, to reach a deeper level of anaesthesia than plane 2. Recovery of consciousness is very rapid, usually within a minute or so from the cessation of the anaesthetic, and is often followed by a light sleep for a period, though postoperative pain will require early treatment.

The postoperative condition of the patients has been most satisfactory even after long operations, and cyclopropane shock did not occur.

The average respiratory rates and minute volumes of children under anaesthesia have been given by Hall (1955) as:

Minute volume	Age	Respiratory rate
3.5 litres per minute	6 months	55 per minute
3.7 ,, ,, ,,	1 year	45 ,, ,,
4.3 ,, ,, ,,	1½ years	43 ,, ,,
4.4 ,, ,, ,,	2 years	30 ,, ,,
4.9 ,, ,, ,,	3 years	31 ,, ,,
5.5 ,, ,, ,,	4 years	30 ,, ,,

It will be seen from table I that the total flow rate of the combined gases, when 10–15 per cent of cyclopropane is given, is materially in excess of the minute volume of infants under 2 years old, thus carbon dioxide accumulation should not occur. There has been no evidence of such accumulation as shown by the absence of excessive bleeding or sweating, bounding pulse or shock. However, when 20 per cent of cyclopropane is given, the total gas flow rate is below the respiratory minute volume of infants over 1 year old. Therefore, using the flow rates recommended, the concentration cyclopropane should not be in excess of 15 per cent for such older infants except for short periods (e.g. to hasten induction of

anaesthesia). Haemorrhage does not appear to be greater than with other methods of anaesthesia.

DISCUSSION

The advantages of this method are:

(1) It is simple and gives a range of anaesthesia suitable for most operations on infants.

(2) A concentration of at least 25 per cent oxygen is assured at all times, while the proportions of the gases delivered to the patient are known and carbon dioxide absorption apparatus is not required.

(3) Induction is rapid and the odour is not unpleasant; there is therefore little breath holding or struggling. Vomiting has not been encountered during maintenance and once only on induction—in a moribund infant with a strangulated hernia.

(4) The plane of anaesthesia can be rapidly varied and is readily recognized by the position and movements of the eyeballs and the depth and character of the respiration. The signs of depth of anaesthesia are clear during induction and maintenance.

(5) Recovery from the anaesthesia is rapid and there is minimal postoperative vomiting and metabolic upset. Feeding can begin within an hour or two if the surgical condition permits.

(6) Light anaesthesia can be maintained for long periods and the infants' normal reactions to stress are probably little impaired. Postoperative shock has not been encountered.

(7) Relaxation is adequate for all operations on neonates. Abdominal relaxation in older infants is variable and is easily obtained by the temporary addition of very small quantities of ether. Controlled respiration can be instituted without difficulty.

(8) Capillary oozing is not marked because, with nitrous oxide and about 25 per cent oxygen, arterialization of the capillaries does not occur, as is seen in closed circuit cyclopropane anaesthesia with higher oxygen concentrations.

(9) The gut tends to be contracted and peristalsis remains active.

(10) With atropine only as premedication and the light levels of anaesthesia obtained, respiration is quiet yet not materially depressed, thereby avoiding carbon dioxide accumulation.

(11) Vagal inhibition has not occurred and is unlikely to do so, as, in addition to atropine premedication, induction is by nitrous oxide and oxygen and the cyclopropane is added gradually and never beyond 20 per cent concentration. Thus respiratory arrest or cardiac irregularities due to deep cyclopropane anaesthesia cannot occur. Stephen and Slater (1950) state: "Cyclopropane is used freely in paediatric anaesthesia. Due to the inherent automaticity of the heart and its freedom from organic lesions in the young, arrythmias or irregularities are seldom produced by this agent."

The disadvantages are:

(1) The mixture is explosive and must not be used when diathermy or other source of ignition is present.

(2) The method is expensive but operations on infants are relatively few and often of short duration.

(3) Respiratory depressant premedication cannot be used.

(4) The possibility of bronchospasm must be envisaged but has not been encountered in this series.

The criteria for anaesthetizing small children, as listed by Stephen and Slater (1950), include: maintenance of as even and light a plane of anaesthesia as is compatible with the surgical procedure; absence of resistance to respiration in the circuit; eradication of mechanical dead space and avoidance of carbon dioxide accumulation; and availability of facilities for assisted respiration.

Rees (1950) states: "On theoretical grounds it is desirable that any technique employed for anaesthetizing young babies should not tend to increase the respiratory volume per minute, and should, if possible, reduce the amount of mechanical energy required for pulmonary respiration. . . . Deep levels of anaesthesia or heavy curarization are not necessary to produce muscular relaxation, because muscle tone is virtually nonexistent in the newborn." Cyclopropane "would seem to be the ideal anaesthetic for neonatal patients" were it not for the excessive loss of blood and postoperative shock.

Griffiths (1952) gives the following advice: "Keep the level of cyclopropane anaesthesia as smooth and even as possible. Cyclopropane will produce quiet, nonirritating relaxing anaesthesia

provided one does not allow the level to fluctuate up and down by careless administration. Unnecessary alterations in the depth of anaesthesia will allow swallowing, vomiting, hypersecretion of mucus, laryngeal spasm, coughing, and abdominal straining."

The method, described above, of cyclopropane anaesthesia by the semiclosed technique, as can be seen from the advantages already listed, satisfies to a large extent the above criteria. In particular, postoperative shock was not observed and the patients reacted to the surgical trauma extremely well. A patient with double cleft lip, aged 9 months, illustrates the absence of undue haemorrhage. The operation took 2 hours and blood replacement was not required: the level of maintenance of anaesthesia was at 15 per cent cyclopropane. Although the number of cases is not large, a wide field of paediatric surgery has been covered.

The method is considered practical and safe for most operations on infants, including major operations of long duration.

Zindler and Deming (1953) consider that the agent of choice for patients with congenital oesophageal atresia is cyclopropane. However, this method has not been tried for such infants on the theoretical grounds that the handling of the mediastinum and the interference with oxygen and carbon dioxide exchange might disturb the action of the heart.

SUMMARY

The methods by which cyclopropane may be used for anaesthetizing infants are mentioned and the critical opinions by various authors are reviewed.

A method of cyclopropane anaesthesia for infants is described. A series of cases on which it has been used is listed, covering a wide range of paediatric surgery.

The advantages and disadvantages of the method are discussed. Criteria for infant anaesthesia by several authors are quoted. It is considered that the method described satisfies, to a large extent, these criteria and that it is practical and safe for most operations on infants including major operations of long duration.

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REFERENCES

Bergner, R. P., and Schafer, G. W. (1956). General Anesthesia for Pediatric Surgery. *Curr. Res. Anesth.*, **35**, 194.

Deming, M. van N. (1952). Agents and Techniques for Induction of Anaesthesia in Infants and Young Children. *Curr. Res. Anesth.*, **31**, 113.

Fairlie, H. (1954). Congenital Atresia of the Oesophagus. The Anaesthetic Problems. *Glasg. med. J.*, **35**, 145.

Griffith, H. R. (1953). How to Stay out of Trouble While Using Cyclopropane. *Curr. Res. Anesth.*, **32**, 23.

Hall, J. E. (1955). Physiology and Respiration in Infants and Young Children. *Proc. roy. Soc. Med.*, **48**, 761.

Hampton, L. J., White, M. L., and Little, D. L. (1952). Anesthesia for Surgical Correction of Cardiorespiratory Anomalies. *Curr. Res. Anesth.*, **31**, 105.

Leigh, M. D., and Belton, M. K. (1950). Special Considerations in the Selection and Employment of Anaesthetic Agents and Methods in Infants and Children. *Anesthesiology*, **11**, 592.

Rees, J. G. (1950). Anaesthesia in the Newborn. *Brit. med. J.*, **2**, 1419.

Shane, S. M., and Ashman, H. (1952). *Sth. med. J. (Bgham., Ala.)*, **45**, 591.

Stephen, C. R. (1952). Technics in Pediatric Anesthesia —The Nonrebreathing Method. *Anesthesiology*, **13**, 77.

—— (1954). *Elements of Paediatric Anesthesia*, 1st ed. p. 72. Illinois: Thomas.

—— Slater, H. M. (1950). Agents and Techniques Employed in Pediatric Anesthesia. *Curr. Res. Anesth.*, **29**, 254.

Wilton, T. N. P. (1952). Anaesthesia for Oesophageal Surgery in Infants and Children. *Curr. Res. Anesth.*, **31**, 267.

Zindler, M., and Deming, M. van N. (1953). The Anesthetic Management of Infants for the Surgical Repair of Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula. *Curr. Res. Anesth.*, **32**, 180.

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A PERSONAL ACCOUNT OF LIGNOCAINE OVERDOSAGE

BY

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INTRODUCTION

SINCE I have been unable to find any record in the literature on the subjective symptoms of lignocaine overdosage by an informed observer, it seemed worth recording the following personal experience.

CLINICAL DETAILS

In preparation for the insertion of pellets, 35 ml of 2 per cent lignocaine (700 mg) was widely infiltrated subcutaneously over the right scapula over a period of ten minutes. Ten minutes later, at the conclusion of the operation, symptoms of overdosage appeared.

OBSERVERS' REPORT

The first symptom was euphoria in which the patient said he felt rather sleepy, but very comfortable and that life was splendid. He also became mildly loquacious and, as the last stitch was being put in, a generalized jactitation occurred. This was of short duration and was not associated with any marked change in pulse or vasoconstriction. The airway remained clear and there was no cyanosis.

Immediately afterwards, he seemed perfectly lucid and the pulse remained steady. Three further jactitations occurred in the next ten minutes. It was noted that just before each fit some phrase was reiterated constantly with mounting excitement. In between, the speech was clear and sensible but there was some scanning. There was also some tremor of the hands.

Sodium thiopentone 150 mg was given which controlled the jactitations, and oxygen was given by a mask. Following the thiopentone, only modified convulsions occurred which were controlled with further doses of 50 mg of thiopentone.

The total duration of the symptoms was about half an hour. At no time was consciousness lost.

SUBJECT'S REPORT

I was lying prone for the operation. During its course I felt rather sleepy, but ascribed this to the fact that I was rather tired that day. Soon I felt slightly drunk, there was a marked intensification of sounds and I felt a little euphoric. The surgeon asked if I was comfortable and I said that it was the most wonderful operation I had ever had. I felt quite unable to stop praising him for the operation.

A little later I felt rather faint and found that my respirations were becoming deeper. The surgeon asked me to breathe normally and as far as I am aware I was able to do this. Then I realized that my hands were twitching; I tried to control this, but was unable to prevent it. I said that I assumed that the effects were all psychological. It was on enunciating the word "psychological" that I realized that I was having some difficulty in pronouncing words.

The surgeon asked me to turn over to the supine position, but I was unable to do this without assistance. I now found that I had to concentrate to talk clearly. I could only speak slowly and it appeared as though everything I said was repeated by another voice in my subconscious. Following this, I found that I had to say each word twice. Associated with this was diplopia which consisted of seeing two sets of eyes vertically above each other and an inability to see anything except in the centre of the visual fields.

The twitching of my hands appeared to increase. I noticed a peculiar sensation of fullness in my head, complete numbness of my forearms and hands, and a dry mouth. At this time there was a marked increase in the intensity of sounds. Everyone seemed to be shouting and I could feel my body shaking.

The feeling of fullness in my head passed off

gradually. I was asked if I felt all right and I said, "Yes." But I noticed that I had to concentrate to prevent myself repeating words. My vision appeared normal, but if I made any sudden movement the diplopia, numbness, repetition of words, and generalized shaking of my body started again.

After a short interval, the symptoms returned; I felt that I had numerous attacks, between which there were short periods in which I felt reasonably well. It was possible to tell when the attacks were developing as each time I noticed a marked intensification of sounds followed by diplopia and double speech.

I remember a longer period of freedom when I asked if I could sit in a chair. I got off the table with assistance and sat down. Shortly afterwards, I complained that blood was pouring down my back; inspection, however, showed no abnormality. In spite of this phenomenon, I felt much better in this position. However, the generalized shaking of my body returned; this appeared worse to me with more marked numbness of my forearms and hands. I had greater difficulty with speaking and had to repeat each word three or four times. The periods of freedom were becoming shorter and the intensification of sounds seemed to be present all the time.

Now I felt my head moving violently from side to side and I found I could only repeat the same word "I" with my voice rising to a shout. Vaguely I remember having been lifted back on to the table. I was told to stop talking and to close my eyes. The latter I was able to do but I had an uncontrollable desire to keep on talking. This seemed a reasonable way to me to prove that I was still alive and also I thought it might help to explain my symptoms.

At one stage when the generalized shaking of my body appeared unduly severe I had a fear of impending doom and I felt an urgent desire to sit up but found myself unable to move.

I heard the instructions for the injection of thiopentone. The skin puncture seemed intensely painful. I remember crying out "No" and repeating it several times. I was told not to worry if I did not sleep following the thiopentone and as far as I am aware I was quite conscious.

Following the thiopentone, my symptoms during the generalized shaking appeared less marked, the attacks shorter and the periods of freedom longer. The numbness passed from my hands and was present only in my feet. The feeling of "fullness" in my head stopped. Eventually, no further attacks occurred and all I noticed was numbness of my toes.

I was ravenously hungry, the only untoward symptoms being marked aching in my arms and neck and feeling cold. This was still pronounced five hours later and I felt a little nausea. Twelve hours later there was still slight aching in my arms and neck.

I would like to stress that throughout the entire period my sense of hearing seemed very acute. Even when unable to speak, I could still seem to hear everything that was said.

DISCUSSION

The cause of the toxic symptoms is not at all clear, but there are certain factors which may have contributed.

The Dose.

Gordh (1949), in his clinical trial with lignocaine in 800 cases, observed no major untoward effects except for two cases of convulsions which received doses of 1.35 and 3.0 g. Hunter (1951) says that lignocaine is twice as toxic as procaine in cats, mice, rabbits and white rats. Graubard et al. (1948) state that the dosage of procaine intravenously for optimal benefits with the least toxic reaction is 4 mg/kg body weight in twenty minutes. My weight is only 54 kg, and hence the amount of lignocaine to be administered should not exceed 108 mg. However, Hunter admits that clinical experience has shown that the toxic dose of lignocaine is considerably in excess of this figure.

In a leading article of the *Journal of the American Medical Association* (1950) it was stated that at a concentration of 0.5 per cent the toxicity of lignocaine was equal to that of procaine in mice, but as the concentration increased the toxicity exceeded that of procaine. It was suggested that at a concentration of 1 per cent it was 40 per cent and at 2 per cent it was 50 per cent greater.

Betlach (1941) states that the toxicity of any local anaesthetic drug increases in geometrical progression with increase in concentration.

However, on three previous occasions I have had a greater quantity of 2 per cent lignocaine infiltrated subcutaneously in the same position without any untoward effects. Admittedly, adrenaline 1:400,000 had been added to these previous doses.

Rate of Absorption.

I had noted on previous occasions that the spread of analgesia was small and the duration short. Previously I had to have further injections given for satisfactory analgesia to be maintained. Hence on this occasion I asked for a wide infiltration to be made.

The toxicity of a drug depends on its blood level. This level is a balance between the rate of absorption, detoxification and the rate of elimination. Collins (1952) states that if adrenaline is added, by causing vasoconstriction it will slow down the rate of absorption. The wide infiltration and absence of adrenaline may have helped to precipitate this attack.

Physical State.

Moore (1955) states that the physical status of a patient may determine, to a marked extent, his susceptibility to reactions from local anaesthetics. For the week prior to the operation I had been rather tired and the night beforehand I had only four hours sleep.

Room Temperature.

It was a very hot day. Collins (1952) states that the rate of absorption and diffusion of a drug increases with a rise in temperature. This might have been a further factor.

Intravenous Injection.

The wide infiltration of volume of the drug injected would make this eventuality possible. It is difficult to assess the time lag between the injection and the onset of toxic symptoms since these were initially indefinite. Thus intravenous injection might have been the cause of the overdosage effects.

Subjective Symptoms.

The peculiar feeling of fullness in my head I find impossible to describe in any clearer form. I should like to emphasize that throughout these toxic effects I was able to hear everything that was said. In fact, my hearing appeared often more acute than normally. This is, I feel, important, since I found that some of the things said by those present alarmed me considerably. Thus, in treating overdosage effects, care should be taken that nothing is said which might alarm the patient.

SUMMARY

A personal account of the subjective phenomena due to a toxic reaction from lignocaine is described. This followed 700 mg of 2 per cent lignocaine subcutaneously. The possible causes are briefly discussed. During the reactions it was noted that hearing was not only unimpaired but seemed intensified.

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REFERENCES

Adriani, J. (1946). Some practical aspects of the chemistry and pharmacology of local anaesthetic drugs. *Sth. med. J. (Bgham, Ala.)*, **39**, 143.

Betlach, C. J. (1941). Methods of local and regional anaesthesia. *Surg. Clin. N. Amer.*, **21**, 277.

Chipps, J. E. (1954). *U.S. armed Forces Med. J.*, **5**, 3.

Collins, U. J. (1952). *Principles and practice of anesthesiology*. Philadelphia: Lea & Febiger.

Geddes, I. C. (1955). Reactions to local anaesthetics. *Canad. med. Ass. J.*, **73**, 828.

Gordh, T. (1949). Xylocaine, a new local anaesthetic. *Anaesthesia*, **4**, 4.

Graubard, D. J., Robertazzi, R. W., and Paterson, M. C. (1947). *Anesthesiology*, **8**, 236.

—— —— —— (1948). *Anesth. et Analg.*, **27**, 222.

Hunter, A. R. (1951).The toxicity of Xylocaine. *Brit. J. Anaesth.*, **23**, 153.

Moore, D. C. (1950). Lignocaine hydrochloride. *J. Amer. med. Ass.*, **142**, 341.

—— (1955). *Complications of regional anaesthesia*. Oxford: Blackwell.

Steinhous, J. E. (1952). Comparative study of the experimental toxicity of local anaesthetic drugs. *Anesthesiology*, **13**, 157.

Zucker, E. (1954). Procaine hydrochloride allergy. *U.S. Armed Forces Med. J.*, **5**, 3, 384.

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A SIMPLE DEVICE FOR AUTOMATIC PRESSURE CONTROL DURING ALTERNATING POSITIVE-NEGATIVE PRESSURE VENTILATION

BY

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IT seems to be generally accepted now that the positive-negative pressure ventilation technique has some advantages whenever artificial respiration is required. These advantages are: (1) An augmentation of venous blood return during expiration; and (2) an overcoming of the resistance to breathing produced by various anaesthetic machines, endotracheal tubes, and stenoses within the respiratory system.

The results of applying negative pressure during expiration are an improvement in blood circulation, a more effective ventilation, and a better gas exchange within the lungs.

One possible disadvantage of the negative pressure is, however, the danger of damaging the lung tissue and producing pulmonary oedema, if a negative pressure of about 8 cm of water is exceeded for any length of time. It is not advisable, therefore, to apply negative pressure to the lungs without any pressure control.

On the other hand, it is not necessary to abstain from using alternating pressure ventilation because none of the more expensive apparatus is available. Controlled positive-negative ventilation may be achieved with any anaesthetic apparatus using a concertina bag and a simple self made water valve arrangement, which is shown (fig. 1) and described here.

The whole equipment consists of four glass tubes of two different diameters, two rubber valves, one concertina bag, one reservoir bag, a suction bottle and a Heron's ball (from a blood pressure apparatus).

The two smaller and narrower glass tubes, equipped each with a rubber valve, are in an airtight manner fixed within the wider tubes. The wider glass tubes are calibrated in cm H_2O (beginning at the lower end of the smaller tubes) and filled with water so that a certain pressure on the inspiratory as well as on the expiratory side cannot be exceeded. By connecting the tubes to a partly waterfilled suction bottle, used here as

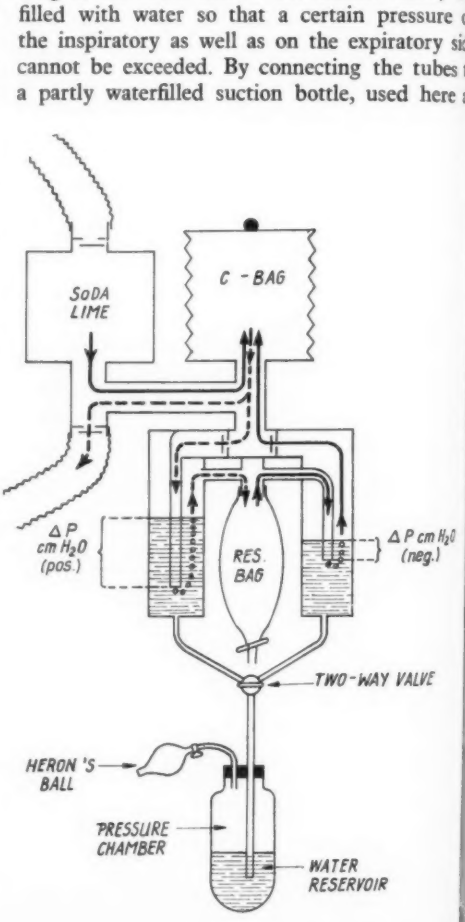

FIG. 1

a pressure chamber, the water levels in the tubes can easily be changed by increasing or diminishing the pressure within the bottle, using a Heron's ball.

The water levels regulate the negative as well as the positive pressure in the respiratory system without needing the anaesthetist's attention once the levels have been adjusted.

On the positive pressure side the wider glass tube is connected to a one-gallon reservoir bag, while on the negative pressure side the smaller tube is connected to the reservoir bag. The reservoir bag will take up gas from the anaesthetic system if the preset positive pressure is exceeded (dotted line), while, on the other hand, gas will be withdrawn from it if the preset negative pressure is exceeded (continuous line). If the reservoir bag becomes too full it can easily be emptied by opening a clamp at its lower end, and if it becomes empty gas can be put back into it by closing the inspiratory tube of the circle system for a moment.

In order to avoid too strong bubbling when exceeding the preset pressures, the narrower glass tubes may be equipped each with a sieve on their lower ends.

Water valves were chosen because they are safer and more easily controllable than other valves. Clamping or leakage of the valves, often seen with any kind of spring valves, can never happen with water valves. Thus the requirements concerning the patient's safety will best be met by using a water valve system for the control of positive and negative pressures during alternating pressure breathing.

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A MODIFICATION OF THE RADCLIFFE PUMP FOR USE IN ANAESTHETIC PRACTICE

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St. Mary's Hospital, Portsmouth

IN any circumstances where the care of cases of respiratory failure is liable to be undertaken using intermittent positive pressure respiration (i.p.p.r.), staff familiar with the use of machines are of great value; the machines themselves are a great boon to the singlehanded anaesthetist. With these two ideas in mind it seemed that a conversion of a small portable respirator to anaesthetic practice would be of some value. The Radcliffe pump seemed the most suitable and easily available machine and accordingly the setup to be described was investigated in clinical anaesthetic practice.

The Radcliffe pump (Russell and Schuster, 1953; Crampton Smith et al., 1954; Russell et al., 1954) is a device in which a concertina bellows is alternatively compressed by weights and expanded by a lifting device. It possesses a pair of valves giving unidirectional flow to its output. As used for the purpose under discussion the output side valve is tripped or the valve disc is removed, and the concertina bellows used to replace the rebreathing bag of a standard circle apparatus (see figs. 1, 3). The ordinary fresh gas intake of the circle is occluded. Fresh gas is led into a reservoir (in this case a lilo pump; A, figs. 1, 2, 3), whence it is led via a wide bore tube to a three-way cock (B, figs. 1, 2, 3); the familiar three-way gas and air cock with the valves removed and the air vent sealed is satisfactory.

This cock provides a variable restriction to the inflow of fresh gas to the circle and is used to modify the suction phase occurring as the bellows is expanded. The third limb of the three-way cock is occluded by a simple spring loaded safety valve (figs. 1, 2C, 3C, 4), through which air is entrained should the negative phase exceed a maximum which can be preset by the anaesthetist.

The circle set-up is attached to the endotracheal

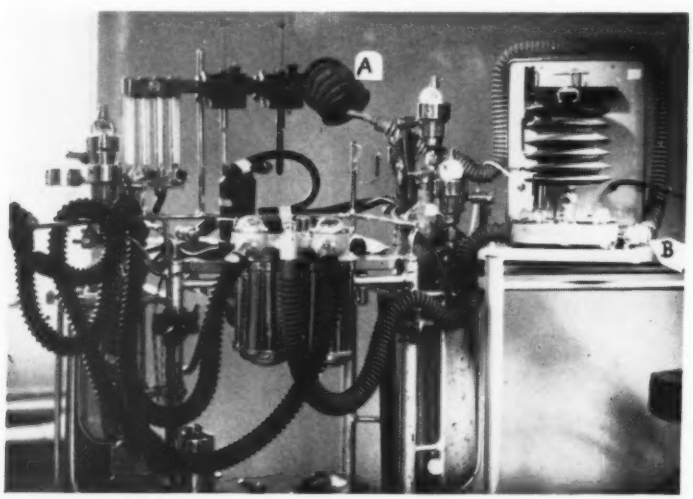


FIG. 1

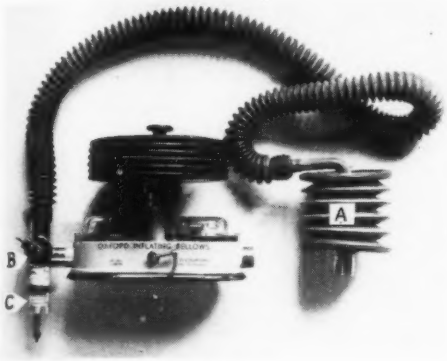


FIG. 2

tube in the usual way, and it is essential that a pressure gauge lead be run off as close to the patient as possible. The usual flow of gases used was from 3 to 4½ l./min of 30 per cent oxygen 70 per cent nitrous oxide, and it is recommended that this sort of flow should be preserved, as the input of fresh gas is sited in such a manner that some may be lost through the expiratory valve before reaching the patient.

During the course of eight different anaesthetics comparison was made between the oxygen content of the gas delivered by the anaesthetic machine and the gas in the afferent limb of the circle close to the endotracheal connection using the oxygen analyser described by Gairdner (1956). Gas was withdrawn into each of two syringes simultaneously via needle punctures in the tube connections. In all 28 comparative determinations were made of which five were regarded as being unsatisfactory; either because of interruption or, in one case, soda lime exhaustion which yields a false high reading for the circle sample. This leaves 23 paired determinations in which no difference could be detected between the oxygen content of gas in either part of the circuit. As the patients remained acapnoeic and there was no alteration in the gas composition throughout the anaesthetics, it has been assumed that carbon dioxide has not in these cases interfered with the analyses.

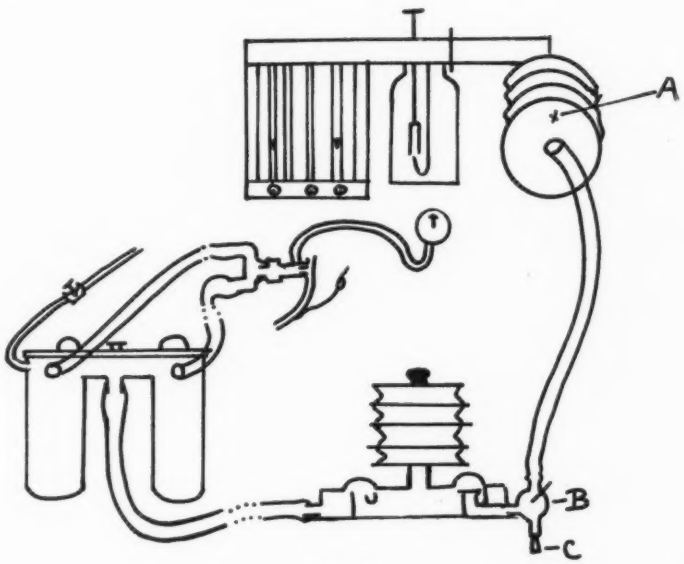


FIG. 3

NOTE: Ether and trichloroethylene bottles empty or removed; pressure gauge lead close to endotracheal mount; normal inflow to circle occluded (easily overlooked).

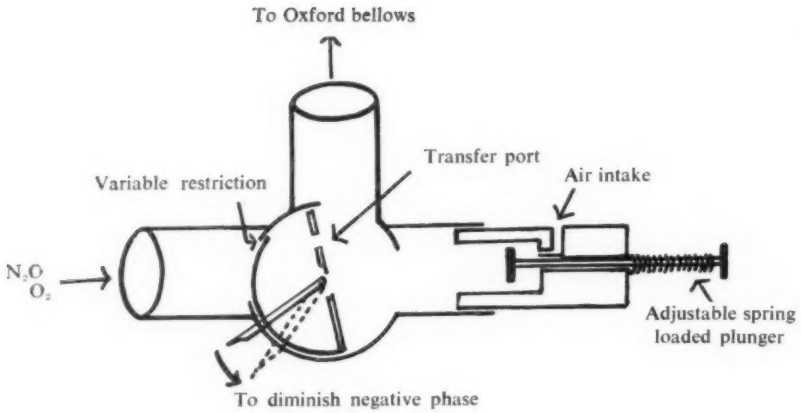


FIG. 4
Assemble correctly or safety valve does not work.

With the pump in use suitable positive pressure is obtained by adjustment of the weights; maintained airway positive pressure is released by using the expiratory valve on the circle, and a balance between the setting of the variable restriction and the expiratory valve is easily achieved to give any desired combination of positive and negative phases. When completely free inflow is allowed, the setting of the expiratory valve determines the airway pressure pattern, and over a fair range gives a positive to zero range of airway pressure. Once a suitable combination of settings has been achieved it is remarkable how constant the performance of the system will remain.

In the early stages of the clinical trials it was noted that in long cases, ill cases and cases with open chests, that the blood pressure tended to fall and that capillary reflux was slowed; this seemed to be reversible with change to hand ventilation or with use of an alternative machine and to recur when the apparatus under discussion was re-employed, using the same minute volume throughout. This effect seemed partially mitigated by use of a negative phase. Obviously there were many variables and using simple clinical methods of observation one cannot be dogmatic, but bearing in mind the work of Werkö (1947), Maloney (1952), and Hubay (1954), it was felt that the airway pressure pattern might be responsible.

Investigation of the airway pressure pattern given by the commercial Radcliffe pump using a simple diaphragm recording manometer showed that the range of ratio inspiration to expiration plus pause working at stroke volumes of about 500 ml was from about 2:3 to 4:3 (see figs. 5, 1a, 1b) with this set-up. This differs considerably from the description given by Garthur Ltd. (1955) in their instruction book.

Using a simple saline manometer as described by Beard (1950) in an article on cardiac catheterization it was noted that in fit patients the venous pressure in the periphery tended to be 1 to 3 cm higher when respired with the apparatus under test than with a machine giving a longer expiratory pause; the number of observations was small, however. In one case with a catheter in the superior vena cava it was found that the venous pressure changes accurately reflected the retained airway positive pressure artificially maintained during the expiratory phase.

One therefore felt that as the pattern of i.p.p.r. did not apparently fall within the range of that recommended in orthodox practice, i.e. that inspiration should be half the time of expiration plus the subsequent pause, and that the clinical picture was not entirely satisfactory, a further modification was proposed.

The device to be described gives an additional range of airway pressure patterns shown in

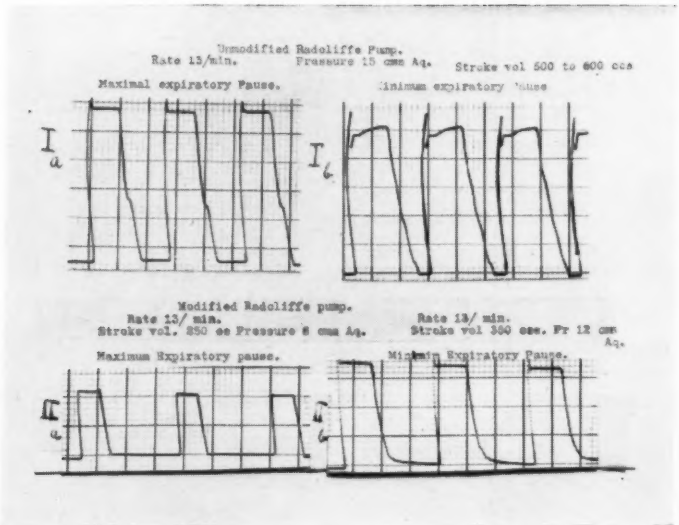

Unmodified Radcliffe Pump.
Rate 13/min.
Pressure 15 cms Aq.
Stroke vol 500 to 600 ccs
Maximal expiratory Pause.
Minimum expiratory Pause
Modified Radcliffe pump.
Rate 13/ min.
Stroke vol. 250 cc Pressure 8 cms Aq.
Rate 13/ min.
Stroke vol 300 ccs. Pr 12 cms Aq.
Maximum Expiratory pause.
Minimum Expiratory Pause.

FIG. 5

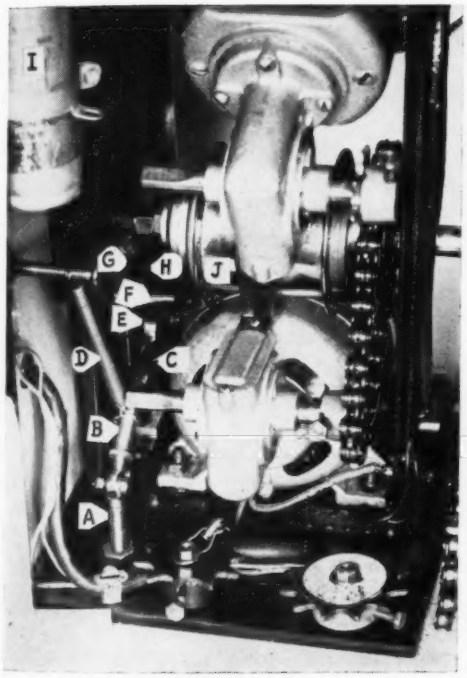


FIG. 6

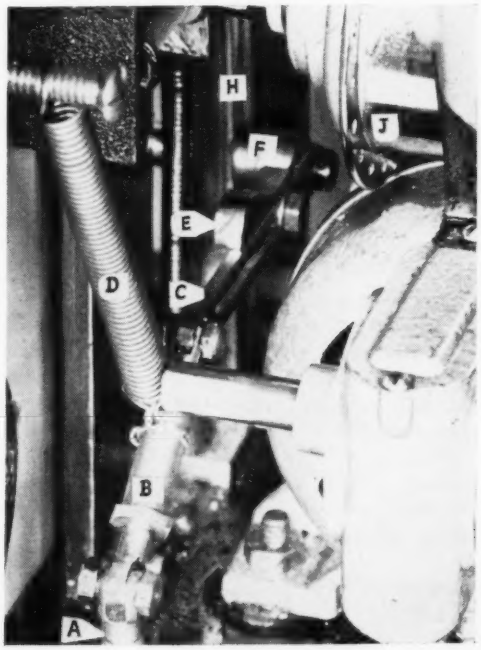


FIG. 7

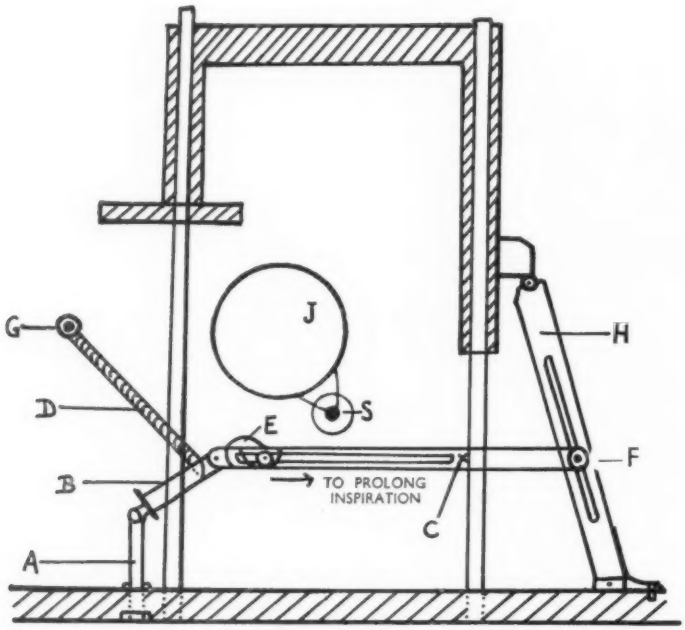


FIG. 8

figure 5, IIa and IIb. The inspiration/expiration plus pause ratio covers the range 1:4 to 1:2.

Referring to figures 6, 7, and 8, the condenser is resited at I. The fixed amount A is bolted through the base plate and is adjustable for height; its upper end has a fork bearing carrying the arm B; a bottle screw adjustable for length. The fork bearing on the arm B articulates with the slotted arm C which carried the cam E. The device F replaces the original striker wheel carrier in the slotted trigger arm H, and has a bearing for the other end of the arm C. The return spring D and its mount G are additional to the return springs fitted at the base of the arm H. In the event of failure of either, the other is adequate for the continued functioning of the machine.

Once suitable lengths of A and B have been selected the only working adjustments are the siting of the cam E on the arm C to give the duration of expiratory pause desired, and its fixture by its locknut, and then the adjustment of the device F along the vertical travel in the slotted arm H so as to bring the cam E into the orbit

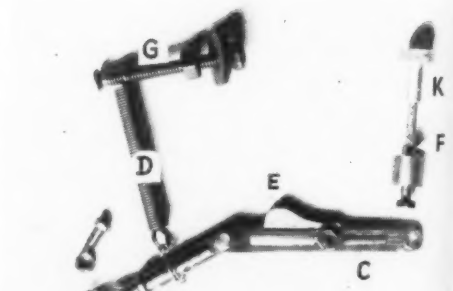
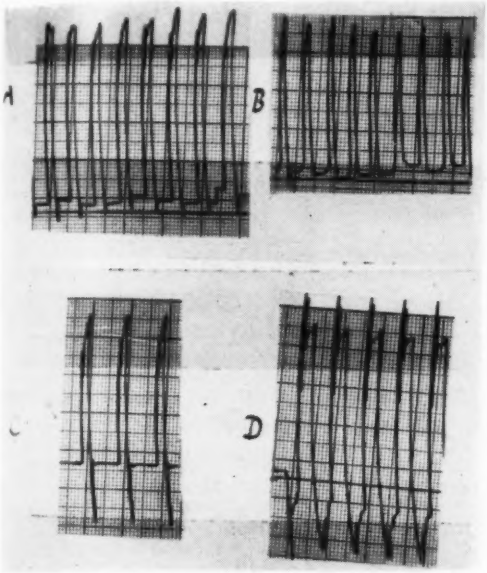


FIG. 9

Hand inflation.
Same patient different anaesthetists.



Blease pulmoflator. Radcliffe pump (standard).

FIG. 10

of the strikers (fig. 8), mounted on the three-speed gear J: and its fixture by the long knurled nut K (fig. 9) which is accessible to the fingers. It is essential that this last adjustment be made with some care; it should be set so that when the cam E is fully depressed the arm H should be fully but not excessively disengaged; should the clearance be inadequate the pump will not function; excessive clearance, on the other hand, will stress the mechanism unduly, although deliberate attempts to break it by maladjustment over about 1,000 cycles were unsuccessful. Care should be taken to tighten the nut K firmly. The farther the cam E is placed from F the shorter will be the duration of inspiration. The nuts on the bearing shafts of the arms B and C and the locknut on the cam E are all No. 2 B.A.; this is the same size as the set bolt retaining the chain sprocket. Thus one spanner suffices for all.

Figure 9 shows the components labelled as in figure 6. They have run on continuous bench test for about three weeks, about 200 hours in anaesthetic practice and about a month in other clinical applications of i.p.p.r.

This additional range of inspiratory/expiratory ratios has been clinically satisfactory in a fair range of patients. One feels it is of particular value in children who clinically seem to be particularly affected by the pattern of i.p.p.r. Harries and Lawes (1956) report a case of particular interest in this connection. The effect of both negative phase and variable inspiratory length can be studied in patients undergoing hypotensive anaesthesia with assurance of thought provoking results.

Figure 10 shows some tracings taken from the airway of a patient undergoing oesophagectomy; A and B are tracings of manual inflation. A maintained airway positive pressure of some 2 cm of water is shown and minor differences of rate and pressure are apparent; the writer can only

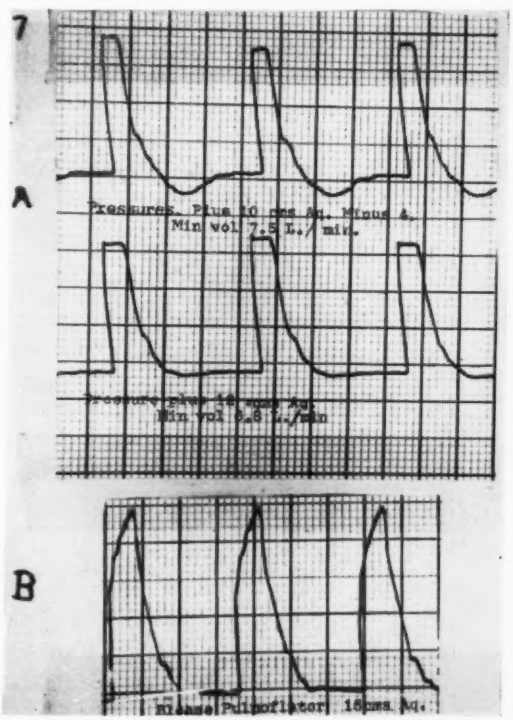


FIG. 11

comment that if he felt capable of maintaining a comparable standard of ventilation manually he would not be as keen on machine respirators as he is. Figure 10, C and D show airway tracings using a Blease pulmoflator and the standard Radcliffe pump in the same patient.

Figure 11 shows tracings from various patients undergoing hysterectomy; in A the modified escapement is in use; in B a comparable minute volume is being obtained using a Blease pulmoflator.

The use of a Parkinson gas meter to monitor the minute volume provided valuable information in that it was found that this set-up tends to produce a large minute volume in anaesthetized patients at modest pressures. Spalding (1955) discusses the relationship of minute volume to applied positive pressure and to duration of inspiration in i.p.p.r.

This apparatus is not suitable for use with potentially explosive anaesthetic mixtures.

SUMMARY

An adaptation of the Radcliffe Pump for use as a positive-negative phase respirator in conjunction with a standard circle anaesthetic apparatus is described. The additional components are easily improvised or cheaply obtained.

A modification of the escapement of the Radcliffe Pump is described which gives an additional shorter range of adjustment to the duration of inspiration. The components were designed and made in a hospital workshop. They are simple and robust.

The apparatus is unsafe for use with explosive agents.

ACKNOWLEDGMENTS

I am much indebted to Dr. H. B. Sandiford for his help and encouragement, to Dr. I. Maclachlan, Physician Superintendent, Portsmouth I.D.H., for the loan of the pump; to Mr. J. Finney and Mr. R. Manning of St. Mary's Hospital, Portsmouth, who engineered the parts; and to Mr. C. Fry, M.P.S., for the photographs.

My thanks are also due to Mr. J. G. O'Sullivan, Mr. R. T. Campbell, and Mr. H. M. Bradmore, during whose operating sessions the clinical work was carried out.

REFERENCES

Ankenney, J. L., Hubay, A. C., Hackett, P. R. and Hingson, R. A. (1954). The Effect of Positive and Negative Pressure Respiration on Unilateral Pulmonary Blood Flow in the Open Chest. *Surg. Gynec. Obstet.*, **98**, 600.

Beard, J. (1950). Cardiac Catheterisation. *Anaesthesia*, **5**, 136.

Cournand, A., Motley, H. I., Werko, L., and Richards, D. W. (1948). Physiological Studies of Intermittent Positive Pressure Breathing on Cardiac Output in Man. *Amer J. Physiol.*, **152**, 162.

Crampton Smith, A., Spalding, J. M. K., and Russell, W. R. (1954). Artificial Respiration by Intermittent Positive Pressure in Poliomyelitis and Other Diseases. *Lancet*, **1**, 939.

Gairdner, D. L. (1956). An Oxygen Analyser. *Lancet*, **1**, 786.

Harries, J. R., and Lawes, W. E. (1956). Intermittent Positive Pressure Respiration. An Unusual Complication in an Infant. *Lancet*, **1**, 783.

Hubay, A. C. (1954). Circulatory Dynamics of Venous Return during Intermittent Positive Negative Respiration. *Anesthesiology*, **15**, 455.

Moloney, J. V., and Whittenburger, J. L. (1951). Clinical implications of pressures used in the body respirators. *Amer. J. med. Sci.*, **221**, 425.

—— Elam, J. O. Handford, S. W., Balla, G. A. Eastwood, B. W., Brown, E. S. and Ten Pas, R. H. (1952). The importance of Negative Phase in Mechanical Respirators. *J. Amer. med. Ass.*, **3**, 213

—— and Handford, S. W. (1954). Circulatory responses to Intermittent positive and alternating positive and negative pressure respiration. *J. appl. Physiol.*, **6**, 453.

Garthur Ltd. (1955). P. P. R. Dir. page 15.

Russell, W. R., and Schuster, E. (1953). Respiration Pump for Poliomyelitis. *Lancet*, **2**, 707.

—— —— Crampton Smith, A., and Spalding, J. M. K. (1956). Radcliffe Respiration Pumps. *Lancet*, **1**, 539.

Spalding, J. M. K. (1955). Pressure and Duration of Inspiration during Intermittent Positive Pressure Respiration. *Lancet*, **1**, 1099.

Werko, L. (1947). The Influence of Positive Pressure Breathing on the Circulation in Man. *Acta med. Scand.*, Sup. 193, 1.

ON CHLOROFORM AND OTHER ANÆSTHETICS

THEIR ACTION AND ADMINISTRATION

BY

JOHN SNOW, M.D.
Licentiate of the Royal College of Physicians

(*Continued from page* 46)

On September 15th 1852, a patient died to whom I was administering whilst Mr. Cæsar Hawkins was performing lithotrity. He was a gentleman from the country, aged seventy-three; he was tall and stout, he had a weak intermitting pulse, and a well marked arcus senilis in each cornea. He had inhaled chloroform five or six times, between May 1850 and May 1851, for the same operation, when under the treatment of another surgeon, and it always acted favourably. In the first week of December 1851, Mr. Hawkins performed the operation of lithotrity twice, when the chloroform was administered by Mr. Geo. D. Pollock. On the second of these occasions he became faint during the operation whilst under the influence of the chloroform, but recovered from the faintness before its conclusion. He again fell into a very alarming state of syncope a few minutes after the conclusion of the operation, but rallied, and vomited the breakfast which he had taken a little time before. I first administered the chloroform to this patient on December 15th, 1851, eleven days after the above occurrence. Mr. Hawkins and I were inclined to think that the alarming syncope on the previous occasion might have been connected with the sickness which occurred. It was my firm belief that the patient had fatty disease of the heart; but I did not see any great objection to the chloroform on that account, as I had frequently given it in similar cases, and always with a favourable result. On this occasion (December 15th) he inhaled the chloroform before breakfast. Its effects were quite satisfactory, and it was not accompanied or followed by any unpleasant symptoms whatever. The operation was repeated four days afterwards, when I again exhibited the chloroform with like favourable results. After this the patient went back to the country relieved from his stone. He came back, however, in the autumn of 1852, with a return of his complaint, and I was again requested by Mr. Hawkins to assist him by giving the chloroform on September 15th.

The patient became insensible, without any excitement or struggling, in the course of three or four minutes, and the operation was commenced. A little more chloroform was administered two or three times during the operation, in order to keep up the insensibility. After a few minutes had elapsed, I observed that the face and lips of the patient became pale. At this time he had not inhaled any chloroform for about two minutes. Immediately afterwards, however, his face became red, and he made straining efforts with the

muscles of respiration, as if he were beginning to feel the operation. To prevent his becoming altogether sensible, therefore, I commenced to give him a little more chloroform, with the valve of the inhaler about one-third open, as on the former occasions. He had only taken two or three inspirations, however, when the breathing ceased. He appeared to be merely holding his breath, as sometimes happens during the exhibition of chloroform, and I expected that he would begin to breathe again in about a quarter of a minute. In the meantime, I endeavoured to feel the pulse in the temporal artery, but did not perceive any. Instead of the breathing recommencing at the time I expected, the countenance became suddenly pale, and a little afterwards rather livid. I applied my ear over the region of the heart, but could not hear any sound. After a few seconds, however, the patient took a rather deep inspiration, and immediately after this I was pretty sure that I heard the heart beating very feebly and rather frequently, but only for a few seconds, after which no sound could be heard. There were one or two more very feeble inspirations at intervals of about a quarter of a minute, after which there were no further signs of life. As soon as the patient had entirely ceased to breathe, artificial respiration was performed, but no sign of returning animation appeared.

At the examination of the body fifty-two hours after death, the heart was found to be larger than natural, and there was a good deal of fat on its surface. Its right cavities contained air or gas, probably resulting from the partial decomposition of the blood. The right ventricle was dilated and its walls were very thin. At one place, near the apex, they were extremely thin. The left ventricle was also dilated, but its walls were of the proper thickness. They were, however, like those of the other ventricle, very soft and friable. There was a calcareous incrustation on one of the aortic valves. There was scarcely any blood in the heart, but its lining membrane was stained in places showing that blood had been present after death.

Mr. Pollock and the late Mr. W. F. Barlow examined the structure of the heart under the microscope, and the latter gentleman furnished me with the following account of the examination: —

"Many of the fibres have been converted into fat completely; in others, fatty degeneration was beginning. The degeneration, which was in various stages, appeared very general. The fasciculi were broken up, here and there, into masses of small irregular fragments, as they may be found frequently in hearts of this kind. Some large fat globules lay between and upon the fibres. A few fibres showed their transverse striæ plainly, and made the changes in the others look the clearer. On the whole, it may be said that the structure of the organ was greatly damaged, and that its action, consequently, was liable to cease suddenly from slight causes."

I am of the opinion that this patient did not die from the direct effects of the chloroform. The air he was breathing just before he died did not contain more than three or four per cent. of vapour of chloroform at the utmost, and he had previously breathed quite as much, both during the same operation and on previous occasions.

The patient seemed to be holding his breath at the moment when his heart ceased to beat; and it is whilst holding the breath and making a straining effort, that patients labouring under disease of the heart not unfrequently expire. Mr. Pollock, who was present when the patient died, expressed to me his belief that he died of his heart disease, and not of the chloroform.

After reflecting on this case, I see no reason to regret the course which was pursued. It was the opinion of Mr. Hawkins that the patient could not have borne the operations without the chloroform; consequently, if we had decided not to permit its use any more, in consequence of the alarming syncope which occurred after the operation under its influence on December 4th, 1851, he would probably have died in great suffering from the calculus, instead of having seven or eight months freedom from the complaint. And, on the other hand, if it had been decided to operate without chloroform, it by no means follows that the patient would have been in less danger, judging from what I have observed of the effect of pain on the circulation, as compared with the effect of the chloroform carefully administered, in numerous other cases of disease of the heart.

On May 11th, 1854, a patient died suddenly in St. George's Hospital as she was beginning to inhale chloroform. She was a pale and delicate looking woman, aged thirty-seven, from whose left breast Mr. Cæsar Hawkins was about to remove a mammary glandular tumour. "On entering the operating theatre she appeared nervous. Having been placed on the table on her back, in a half reclining position, the administration of chloroform was commenced. Dr. Snow's inhaler was used. The quantity of chloroform placed in the receiver was little more than a drachm; and the valve for the admission of air was left wide open. Apparently, from excitement, she did not inhale well, but drew her breath by deep catches, and irregularly. Mr. Potter, noticing this, spoke to her, begging her to compose herself, and try to breathe more quietly. The valve was then slightly turned on, in order that she might inhale but a very small quantity of chloroform. The same spasmodic efforts at inspiration still continued; very shortly afterwards, at most not more than a minute and a half from the commencement of the inhalation, Mr. Potter noticed her breathing to suddenly cease, and that she had become deathly pale. The inhaler was at once removed. On placing the finger on the wrist, no pulse could be found. Endeavours to arouse her by dashing the face and chest with water were immediately adopted; but, proving ineffectual, artificial respiration was commenced within a minute of the first symptoms. During the interval, two sighing attempts at inspiration had been observed; but there had been no pulse whatever; the mouth lay a little open, and the countenance was still extremely pale.* Other attempts at resuscitation were made without effect.

"At the post-mortem examination, on the following day, no very noticeable lesions of the viscera were discovered. There was congestion of the whole venous system, and the blood, in every organ, was

* Medical Times and Gazette, 1854, vol. i, p. 516.

of a deep purple colour, and quite fluid. The brain-substance itself was perhaps a little more vascular than usual, and the veins of its meninges were loaded with blood. The heart was small and fat, the right ventricle being especially loaded with adipose material, and its muscular layer much thinned. Under the microscope there was found to be slight, yet decided, fatty degeneration of the muscular structure. Both chambers, but more particularly the right, were distended with blood in which no coagula could be found. The posterior lobes of the lungs were somewhat congested, but not more than the position in which the corpse had lain might account for. There was no disease of the abdominal viscera.*

I made a chemical examination of some blood obtained from the heart and large vessels, and also of portions of the lungs and liver, but I failed to detect any trace of chloroform, although the process I employed is one by which I have very easily detected it in the bodies of small animals killed by it, and also in portions of limbs and tumours removed whilst the patients were under its influence to the usual extent.

It was impossible that this patient could have breathed air strongly charged with vapour. Every one in the operating theatre was a witness that the expiratory valve of the face-piece was not, at any time, more than one-third closed, being two-thirds open. In this way no great effect of any kind can be produced, as very little of the air which the patient breathes passes through the inhaler. Mr. Potter informed me, moreover, that the patient breathed very little even of air, her breathing was so much embarrassed by her frightened condition. He was trying to calm her apprehensions at the moment when she died.

The mental emotion under which the patient was labouring was, no doubt, the cause of the sudden death in this instance, as in that above referred to, which occurred at Mr. Robinson's. The mode of dying, in the present instance, was evidently by cardiac syncope; the same mode of death, in fact, as that which is occasioned by vapour of chloroform, when not sufficiently diluted; and it is only the absolute knowledge that any small quantity of vapour which this patient inhaled was very largely diluted with air, that enables one to decide, with confidence, that the chloroform was not the cause of death. It may be observed, however, that there was an absence of the convulsive start or spasm which occurred in all those deaths from chloroform which took place at the beginning of the inhalation, without loss of consciousness having been first induced.

The right cavities of the heart were found full of blood in this case, and it is probable that they became so much distended, as the patient was in a state of alarm, and scarcely breathing, that, in the thin and diseased state of the walls of the right ventricle, the action of the heart was arrested. Sudden death not unfrequently takes places during mental emotion, and, in many of the cases, the mode of dying is probably that just mentioned.

* Ibid., p. 517.

(*To be continued*)

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